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ALIMTA®
pemetreksed

Pravi **Izbor**
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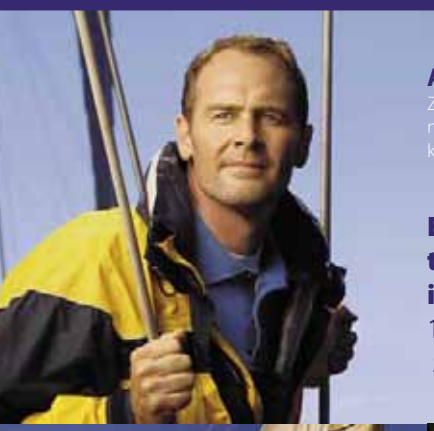
Pravi **Čas**

Edina histološko usmerjena citostatična terapija



ALIMTA/cisplatin:
Zdravljenje prvega reda pri bolnikih z nedrobnoceličnim pljučnim karcinomom, ki nimajo pretežno luskaste histologije

Edina kombinirana terapija s signifikantno izboljšanim preživetjem:
12,6 meseca pri bolnikih z adenokarcinomom pljuč[1]

*vs, Gemcitabine/Cisplatin
1. Scagliotti GV et al, Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3543-51.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Ime zdravila ALIMTA 100 mg prašek za koncentrat za raztopino za infundiranje in ALIMTA 500 mg prašek za koncentrat za raztopino za infundiranje **Kakovostna in količinska sestava** ALIMTA 100 mg: vsaka viala vsebuje 100 mg pemetrekseda (v obliki dinatrijevega pemetrekseda). Po pripravi vsebuje vsaka viala 25 mg/ml pemetrekseda. Pomožne snovi: Vsaka viala vsebuje približno 11 mg natrija. Manitol, klorovodikova kislina, natrijev hidroksid. ALIMTA 500 mg: vsaka viala vsebuje 500 mg pemetrekseda (v obliki dinatrijevega pemetrekseda). Po pripravi vsebuje vsaka viala 25 mg/ml pemetrekseda. Pomožne snovi: Vsaka viala vsebuje približno 54 mg natrija. Manitol, klorovodikova kislina, natrijev hidroksid. **Terapevtske indikacije: ALIMTA je v kombinaciji s cisplatinom indicirana za zdravljenje bolnikov z neresektabilnim malignim plevralnim mezoteliomom, ki jih še nismo zdravili s kemoterapijo. ALIMTA je v kombinaciji s cisplatinom indicirana kot zdravljenje prvega izbora za bolnike z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom, ki nima pretežno luskaste celične histologije. ALIMTA je indicirana kot monoterapija za zdravljenje lokalno napredovalega ali metastatskega nedrobnoceličnega pljučnega karcinoma, ki nima pretežno luskaste celične histologije pri bolnikih, pri katerih bolezen ni napredovala neposredno po kemoterapiji na osnovi platine. Zdravljenje prvega izbora naj bo platinasta dubleta z gemcitabinom, paklitakselom ali docetakselom. ALIMTA je indicirana kot monoterapija za zdravljenje drugega izbora bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom, ki nima pretežno luskaste celične histologije. Odmerjanje in način uporabe:** ALIMTO smemo dajati le pod nadzorom zdravnika, usposobljenega za uporabo kemoterapije za zdravljenje raka. ALIMTA v kombinaciji s cisplatinom Priporočeni odmerek ALIMTE je 500 mg/m2 telesne površine (TP), dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21-dnevnega ciklusa. Priporočeni odmerek cisplatina je 75 mg/m2 TP, infundiran v dveh urah približno 30 minut po zaključku infuzije pemetrekseda prvi dan vsakega 21 dnevnega ciklusa. Priporočeni odmerek cisplatina je 75 mg/m2 TP, infundiran v dveh urah približno 30 minut po zaključku infuzije pemetrekseda prvi dan vsakega 21 dnevnega ciklusa. Bolniki morajo prejeti zadostno antiemetično zdravljenje, pred in/ali po prejemanju cisplatina jih moramo tudi ustrezno hidrirati. ALIMTA kot samostojno zdravilo Priporočeni odmerek ALIMTE je 500 mg/m2 TP, dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21 dnevnega ciklusa. Režim premedikacije Da zmanjšamo incidenco in resnost kožnih reakcij, dajemo kortikosteroid dan pred dajanjem pemetrekseda, na dan dajanja pemetrekseda in naslednji dan. Kortikosteroid naj ustreza 4 mg deksametazona, danega peroralno dvakrat dnevno. Za zmanjšanje toksičnosti morajo bolniki dnevno jemati tudi peroralno folno kislino ali multivitaminski pripravek, ki jo vsebuje (350 do 1000 mikrogramov). V sedmih dneh pred prvim odmerkom pemetrekseda morajo vzeti vsaj pet odmerkov folne kisline, odmerjanje pa morajo nadaljevati ves čas zdravljenja in še 21 dni po zadnjem odmerku pemetrekseda. Bolniki morajo prejeti tudi intramuskularno injekcijo vitamina B12 (1000 mikrogramov) v tednu pred prvim odmerkom pemetrekseda in enkrat vsake tri cikluse zatem. Kasnejše injekcije vitamina B12 lahko dajemo isti dan kot pemetreksed. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Dojenje. Sočasno cepljenje proti rumeni mrzlici **Posebna opozorila in previdnostni ukrepi:** Pemetreksed lahko zavre delovanje kostnega mozga, kar se kaže kot nevtropenija, trombocitopenija in anemija (ali pancitopenija). Pri bolnikih, ki pred zdravljenjem niso prejemali kortikosteroidov, so poročali o kožnih reakcijah. Uporabe pemetrekseda pri bolnikih z očistkom kreatinina < 45 ml/min ne priporočamo. Bolniki z blagim do zmernim popuščanjem delovanja ledvic naj se izogibajo jemanju nesteroidnih protivnetnih zdravil (NSAID), denimo, ibuprofena in acetilsalicilne kisline 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Vsi bolniki, ki jih lahko zdravimo s pemetreksedom, naj se izogibajo jemanju NSAID-ov z dolgimi razpolovnimi časi izločanja vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Poročali so o resnih ledvičnih primerih, vključno z akutno ledvično odpovedjo, s pemetreksedom samim ali v povezavi z drugimi kemoterapevtiki. Pri bolnikih s klinično pomembno tekočino tretjega prostora moramo razmisliti o drenaži izliva pred dajanjem pemetrekseda. Kot posledico toksičnosti pemetrekseda v kombinaciji s cisplatinom za prebavila so opažali hudo dehidracijo, zato moramo bolnike pred prejemanjem terapije in/ali po njej ustrezno hidrirati, prejeti morajo zadostno antiemetično zdravljenje. Občasno so v kliničnih študijah pemetrekseda, običajno ob sočasnem dajanju z drugo citotoksično učinkovino, poročali o resnih srčnožilnih dogodkih, vključno z miokardnim infarktom in možganskožilnimi dogodki. Odsvetujemo uporabo živih oslabljenih cepiv. Spolno zrelim moškim odsvetujemo zapodetev otroka v času zdravljenja in še 6 mesecev zatem. Priporočamo ukrepe prosti zanositvi ali vzdržnost. Zaradi možnosti, da zdravljenje s pemetreksedom povzroči trajno neplodnost, naj se moški pred začetkom zdravljenja posvetujejo o shranjevanju semena. Ženske v rodni dobi morajo v času zdravljenja s pemetreksedom uporabljati učinkovito kontracepcijo. Poročali so o primerih radiacijske pljučnice pri bolnikih, ki so jih zdravili z radiacijo pred, med ali po zdravljenju s pemetreksedom. Poročali so o radiacijskem izpuščaju pri bolnikih, ki so se zdravili z radioterapijo pred tedni ali leti. Zdravilo Alimta 500 mg vsebuje približno 54 mg natrija na vialo. Pomembno za bolnike, ki so na dieti z nadzorovanim vnosom natrija. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno dajanje nefrotoksičnih zdravil (denimo, aminoglikozidov, diuretikov zanke, spojin platine, ciklosporina) lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Sočasno dajanje snovi, ki se tudi izločajo s tubulno sekrecijo (denimo, probenecid, penicilin), lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Pri bolnikih z normalnim delovanjem ledvic lahko visoki odmerki nesteroidnih protivnetnih zdravil (NSAID-i, denimo, ibuprofen) in acetilsalicilna kislina v visokih odmerkih zmanjšajo eliminacijo pemetrekseda in tako lahko povečajo pojavnost neželenih učinkov pemetrekseda. Pri bolnikih z blagim do zmernim popuščanjem delovanja ledvic se moramo izogibati sočasnemu dajanju pemetrekseda z NSAID-i (denimo, ibuprofenom) ali acetilsalicilne kisline v visokih odmerkih 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Sočasnemu dajanju NSAID-ov z dalјšimi razpolovnimi časi s pemetreksedom se moramo izogibati vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Velika različnost med posamezniki v koagulacijskem statusu v času bolezni ter možnost medsebojnega delovanja med peroralnimi antikoagulacijskimi učinkovinami ter kemoterapijo proti raku zahtevata povečano pogostnost spremljanja INR. **Kontraindicirana sočasna uporaba:** Cepivo proti rumeni mrzlici: tveganje za smrtno generalizirano bolezen po cepljenju. **Odsvetovana sočasna uporaba:** Živa oslabljena cepiva (razen proti rumeni mrzlici): tveganje za sistemsko, potencialno smrtno bolezen. **Neželeni učinki** Klinične študije malignega plevralnega mezotelioma *Zelo pogosto:* znižani nevtrofilci/granulociti, znižani levkociti, znižan hemoglobin, znižani trombociti, nevropatija-senzorična, diareja, bruhanje, stomatitis/faringitis, slabost, anoreksija, zaprtje, izpuščaj, alopecija, povišan kreatinin, znižan očistek kreatinina, utrujenost. *Pogosti:* dehidracija, motnje okusa, konjuktivitis, dispepsija. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija, zdravljenje 2. izbora: *Zelo pogosti:* znižan nevtrofilci/granulociti, znižani levkociti, znižan hemoglobin, diareja, bruhanje, stomatitis/faringitis, slabost, anoreksija, izpuščaj/luščenje, utrujenost. *Pogosti:* znižani trombociti, zaprtje, povišanje SGPT (ALT), povišanje SGOT (AST), srbenje, alopecija, povišana telesna temperatura. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA v kombinaciji s cisplatinom, zdravljenje 1. izbora: *Zelo pogosti:* znižan hemoglobin, znižani nevtrofilci/granulociti, znižani levkociti, znižani trombociti, slabost, bruhanje, anoreksija, zaprtje, stomatitis/faringitis, diareja brez kolostomije, alopecija, izpuščaj/luščenje, povišan kreatinin. *Pogosti:* nevropatija-senzorična, motnje okusa, dispepsija/zgaga. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija, vzdrževalno zdravljenje: *Zelo pogosti:* znižan hemoglobin, slabost, anoreksija, utrujenost, izpuščaj/luščenje, utrujenost. *Pogosti:* infekcija, znižani levkociti, znižani nevtrofilci, nevropatija-senzorična, bruhanje, mukozitis/stomatitis, diareja, povišanje ALT (SGPT), povišanje AST (SGOT). Občasno so v kliničnih študijah pemetrekseda poročali o primerih resnih srčnožilnih in možganskožilnih dogodkov, vključno z miokardnim infarktom, angino pektoris, cerebrovaskularnim insultom in prehodnimi ishemičnimi atakami; primerih kolitisa ter o primerih interstic̆ijske pljučnice z respiratorno insuficience, primerih edema in o ezofagitisu/radiacijskem ezofagitisu. Redkeje pa o primerih potencialno resnega hepatitisa in pancitopenije. Po uvedbi zdravila na trg so poročali o primerih akutne odpovedi ledvic s pemetreksedom samim ali v povezavi z drugimi kemoterapevtiki, primerih radiacijske pljučnice pri bolnikih, ki so jih zdravili z radiacijo pred, med ali po njihovem zdravljenju s pemetreksedom, primerih radiacijskega izpuščaja pri bolnikih, ki so se v preteklosti zdravili z radioterapijo in o primerih periferne ishemije, ki je včasih vodila v nekrozo okončin. **Imetnik dovoljenja za promet** Eli Lilly Nederland B.V., Grootslag 1 S, NL 3991 RA, Houten, Nizozemska. Datum zadnje revizije besedila 21.09.2009
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Eli Lilly Farmacevtska družba, d.o.o.
Brničičeva 41G, 1231 Ljubljana - Črnuče, Slovenija
Telefon: +386 (0)1 5800 010
Faks: +386 (0)1 5691 705

Lilly

RADIOLOGY AND ONCOLOGY

Editorial office
Radiology and Oncology
Institute of Oncology
Zaloška 2
SI-1000 Ljubljana
Slovenia
Phone: +386 1 5879 369
Phone/Fax: +386 1 5879 434
E-mail: gsersa@onko-i.si

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review

Radiotherapy in palliative treatment of painful bone metastases

Andreja Gojkovič Horvat, Viljem Kovač, Primož Strojan

Department of Radiation Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background. *Pain caused by bone metastases is the most common symptom requiring the treatment in cancer patients. Bone metastases often present as the first evidence of disseminated disease, the most common primary sites being breast, prostate, and lung. Important in palliative treatment is to reach a maximal effect with the minimal treatment. The aim of palliation for cancer patients is to increase the quality of their remaining life.*

Conclusions. *The management of bone pain includes analgesics, local treatment (radiation, surgery) and systemic treatment (hormones, chemotherapy, radioisotopes and agents such as bisphosphonates). The treatment of bone cancer pain often requires a multidisciplinary approach. Radiotherapy remains the most important palliative treatment for localized bone pain. The treatment duration can generally be reduced to a single treatment with excellent and long-lasting palliative analgesic responses. The treatment should be individualized according to the patient's clinical condition and life expectancy.*

Key words: bone metastases; palliative treatment; radiotherapy

Introduction

Pain caused by bone metastases is the most common symptom requiring the treatment in cancer patients and they often present as the first evidence of disseminated disease.[1] About three quarters of patients with the end-stage disease will eventually need the pain management.[2] Bone metastases are common in patients suffering from many types of cancer with systemic dissemination, especially breast cancer, prostate and lung cancer, with the incidence of approximately 70%, 70% and 35%, respectively.[3] Lesions occurring in breast, lung, prostate and kidney comprise 80% of all metastases to bone.[4] Bone metastases are associated with considerable skeletal morbidity, including severe bone pain, spinal cord or nerve root compression, pathological fractures and hypercalcaemia.[5-9]

Although the skeleton receives only 10% of the cardiac output, metastases in the skeleton are very common as compared to metastases to other tissues receiving a far greater amount of the cardiac output.[10] The bone metastases are found almost invaria-

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Correspondence to: Andreja Gojkovič Horvat, M.D., Department of Radiation Oncology, Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia. Phone: +386 1 5879 110; Fax: + 386 1 5879 400; E-mail: agojkovic@onko-i.si

bly in the red marrow, and the bones most frequently involved are those with a high proportion of red marrow.[5,11] Thus, more than 80% of bone metastases are found in the axial skeleton.[2,6]

Bone metastases can be of osteolytic types (increase bone destruction), osteosclerotic types (increase bone formation), or mixed types. Osteolytic metastases are the predominant types of lesions in most cancers, but a sclerotic appearance is seen in the majority of prostate cancer metastases.[5]

Pain caused by bone metastases or from the invasion of the tumour in the bone is frequently the first symptom for which the patients will seek advice.[7,12,13] In general, there are two types of pains in patients with bone metastases. The first type is a continuous pain and is usually described as a dull aching pain that increases in severity over time. The second type of bone cancer pain is movement-evoked, breakthrough or episodic and is more acute in nature.[14]

Important in the palliative treatment is to reach a maximal effect with the minimal treatment. In cancer patients with systemic metastases and thus limited life expectancy, the aim of palliation is to increase the quality of their remaining life.

Different modalities in palliative therapy of bone metastases

The treatment of bone metastases requires a broad approach.[15] The reduction of pain is its major goal. Also, of great importance are the prevention of possible fractures and the improvement of mobility.[1]

The management of bone pain includes analgesics, local treatment (radiation, surgery) and systemic treatment (hormones, chemotherapy, radioisotopes and agent such as bisphosphonates).[1,16] Therefore, the treatment of bone cancer pain often requires a multidisciplinary approach.[17]

Analgesics

The control of bone pain usually begins with analgesics used in a 3-step approach. To relieve mild to moderate pain non-opioid analgesics (the first step) are initially used. With persistence or increase in pain when using non-opioid analgesics only, the treatment progresses to utilize weak opioides (the second step) changing to higher doses or more potent opioids (the third step), if the pain persists or becomes more severe.[17-19] These more potent opioids have significant side effects (constipation and lethargy are particularly common).

To limit the dose of opioids and their side effects, radiotherapy and sometimes surgery (*i.e.* no evidence of metastatic disease elsewhere in the body with primary tumour control) are used for the treatment of localised metastases.[16-19]

Radiation therapy

Most commonly, radiotherapy is used to provide pain relief for the painful bone metastases. It is an effective and safe non-invasive palliative treatment.[17,18]

The radiation treatment includes the local radiation when the disease is localized and the systemic one in more diffusely disseminated disease. The systemic radiation takes account of half-body irradiation (HBI) and therapy with radioisotopes.[1]

Local radiotherapy

Radiotherapy remains the most important palliative treatment for localized bone pain.[20] A number of randomized trials have been carried out and substantial proportion

of them were done on highly selected populations of patients due to the varying clinical presentation of bone metastases.[20-22]

In these trials, radiotherapy was reported to produce a complete pain relief at one month in 25% of patients. A pain relief at least 50% (*i.e.* partial response) at one month was achieved in 41% of patients.[20] However, the transient pain flare is common after the palliative radiotherapy for osseous metastases.[23] Hird *et al.*[24] found out that patients treated with a single 8 Gy reported a pain flare incidence of 39% and, after using multiple fractions, 41%. A further studies are warranted to determine predictors and necessary preventive interventions.[23,24]

The prospective randomized trials compared the effect of a single fraction (mostly of 8 Gy) to different multifraction regimen and different single fraction irradiation doses to themselves.[20-22,25-42] It was important that – on general – a single fraction of 8 Gy is equivalent to multiple fractions in quality and duration of pain relief (Table 1).

However, there is still questionable, if 8 Gy is the optimal single fraction dose.[30] Results of at least two single institution clinical studies indicate that 8 Gy could be considered as probably the "lowest" single fraction dose to be used in palliative setting in the treatment of painful bone metastases, although the single fraction radiotherapy of 4 Gy should not be simply discarded due to its applicability in specific cases.[31,34]

The only difference between the single fraction and the multifraction regimen observed was in the rate of re-treatment and in the rate of the pathological fracture. More patients from a single fraction group require the re-treatment.[25,36,37,41] In spite of an opinion, that the decision to re-treat a patient might be influenced by other factors, *i.e.* physician bias[43], a systemic review of randomised trials and meta-analysis confirmed that the re-treatment rate and the pathological fracture rate were higher after the single fraction radiotherapy.[21,22] On the other hand, one must be aware that discrepancies may exist between meta-analyses and individual large randomized, controlled trials.[44] Therefore, the most recent randomised studies only are to be considered. However, they are still controversial. For example, Roos *et al.*[38] reported the results of a TROG 96.05 trial, where no statistically significant difference in the rate of re-treatment procedures, cord compressions or pathological fractures was observed across different treatment groups, whereas Foro Arnalot *et al.*[26] proved that the re-treatment was more frequent in the arm with a single fraction irradiation.

Jeremic *et al.*[45] were investigating the effectiveness of a 4 Gy single-fraction re-treatment regimen for painful bone relapse after previous single-dose radiotherapy with 4 Gy, 6 Gy and 8 Gy. It is of note that after the re-irradiation the response rate was 74% and 46% of responses was recorded in previously non-responding patients. There was no difference in response according to the initial dose.

Results of prospective randomized trials comparing two different multifraction radiation schedules also confirmed that the irradiation with fewer fractions was as effective as the more prolonged regimens. However, shorter radiation schedules were proved to be more convenient to the patient and of less cost to the society.[29,39,40,42]

In the cases when pain is the first symptom of developing paraparesis radiotherapy is of crucial importance. However, when the spinal cord compression is suspected, high-dose corticosteroids should be administered and whole-spine magnetic resonance imaging scan performed as soon as possible but not later than 24 hours from the start of neurological deficit. Definitive treatment for diagnosed cord compres-

Table 1. Results of published randomized controlled clinical trials on dose and fractionation pattern for palliation of painful bone metastases. (Only trials with more than 100 patients enrolled listed in the table)

Reference	Comparison*		Number of patients Randomised	Primary endpoint p-value**
Bone Pain Trial Working Party, 1999[25]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 5 fractions or 30 Gy in 10 fractions	761	n.s.
Foro Arnalot P *et al.*, 2008[26]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	160	n.s.
Gaze MN *et al.*, 1997[27]	A: B:	10 Gy in 1 fraction *vs* 22.5 Gy in 5 fractions	280	n.s.
Hartsell WF *et al.*, 2005[28]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	898	n.s.
Hirokawa Y *et al.*, 1988[29]	A: B:	25 Gy in 5 fraction *vs* 30 Gy in 10 fractions	182	n.s.
Hoskin PJ *et al.*, 1992[30]	A: B:	4 Gy in 1 fraction *vs* 8 Gy in 1 fractions	270	n.s.
Jeremic B *et al.*, 1998[31]	A: B: C:	4 Gy in 1 fraction *vs* 6 Gy in 1 fraction *vs* 8 Gy in 1 fraction	327	A<B: p<0.025 A<C: p<0.0019
Kaasa S et al., 2006[32]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	376	n.s.
Kirkbridge P *et al.*, 2000[33]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 5 fractions	398	A<B: p=0.03
Koswig S *et al.*, 1999[34]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	107	n.s.
Ma as A *et al.*, 2008[35]	A: B:	6 Gy in 1 fraction*** *vs* 8 Gy in 1 fraction***	118	A<B: p=0.0211
Nielsen OS *et al.*, 1998[36]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 4 fractions	241	n.s.
Price P *et al.*, 1986[37]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	288	n.s.
Roos DE *et al.*, 2005[38]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 5 fractions	272	n.s.
Quilty PM *et al.*, 1994[39]	A: B: C:	Hemibody irradiation 6 Gy in 1 fraction *vs* Local irradiation 20 Gy in 5 fractions *vs* 89-Sr 200 MBq	284	n.s.
Rasmusson B *et al.*, 1995[40]	A: B:	15 Gy in 3 fractions *vs* 30 Gy in 10 fractions	217	n.s.
Steenland E *et al.*, 1999[41]	A: B:	8 Gy in 1 fraction *vs* 24 Gy in 6 fractions	1171	n.s.
Tong D *et al.*, 1982[42]	A: B:	20 Gy in 5 fractions *vs* 40.5 Gy in 15 fractions	266	n.s.
Total			**6616**	

*Gy – unit of dose, Gray; **n.s. – not significantly different at the 5% level;
***patient were treated also with zolodronic acid.

sion– surgical decompression or urgent radiotherapy – should be initiated within 24 hours.[9,18] The early recognition of the *symptoms* and a prompt diagnosis are essential for the onset of the optimal therapy.[46]

In conclusion, the single-fraction radiotherapy of 8 Gy should be a standard management policy for patients with painful bone metastases.[32] In clinical practice, however, with a single fractions more frequently are irradiated the older patients; those with more weight loss and poor performance status or with progressive local disease and/or widely disseminated disease elsewhere in the body. Pelvis, long bones and chest wall are more frequent irradiated with single fractions.[47] Compared with multiple-fraction radiotherapy, single-fraction regimen is equally effective when quality of life measures are studied, but, for lower medical and societal costs. Therefore, single-fraction radiotherapy should be considered as the palliative treatment of choice for majority of cancer patients with painful bone metastases.[48,49]

Half-body irradiation (HBI)

HBI is used in patients with widely metastatic disease when large segment of the body is to be irradiated. With this technique the irradiation dose can be delivered as a single fraction or through several smaller fraction doses.[50,51]

Three types of HBI fields have been described.[52] They are as follows: *(1)* Upper half-body irradiation (UHBI) – irradiation field encompasses the area from the level of mastoid process to the level of the iliac crest (L4-L5 interface or the umbilicus); *(2)* Lower half-body irradiation (LHBI) – upper border of irradiation field is placed at the lower edge of the upper HBI field (L4-L5 interface) and the lower border at the ankles; and *(3)* Midportion-body irradiation (MBI) – irradiation field extend from the top of the diaphragm to the bottom of the obturator foramina.

To date, single-dose HBI was one of the safest, fastest and most effective palliative tools in the treatment of cancer pain.[52]

As not being without any toxicity, the irradiated patients require either a one-day hospitalization or close monitoring several hours after the procedure.[51] A comprehensive premedication program has proven to decrease the acute radiation syndrome to an acceptable level.

The effectiveness and the safety of the single-doses HBI of different dose levels in patients with multiple bone metastases were analysed in RTOG 78-10 study.[52] The most effective and harmless HBI regimen tested were 6 Gy-regimen for the UHBI and 8 Gy-regimen for the LHBI or MBI. The increase in dose was associated with an increase in toxicity such as pneumonitis in UHBI and gastrointestinal upset in the LHBI or MBI. The bone marrow toxicity was maximal at 2 weeks post-HBIand its regeneration was seen in 4 to 6 weeks. HBI was found to relieve pain in 73% of irradiated patients and in as much as 20% of thm the pain relief was complete. Over two thirds of all patients achieved better than 50% pain relief. The HBI pain relief was dramatic with nearly 50% of all responding patients doing so within 48 hours and 80% within one week from HBI treatment.[52]

This treatment is somewhat toxic and the patients required either a one-day hospitalization or close monitoring several hours after the procedure.[51] A comprehensive premedication program has proven to decrease the acute radiation syndrome to acceptable levels.

To date, single-dose HBI was one of the safest, fastest and more effective palliative tools in the treatment of cancer pain.[52]

In comparison with single-dose HBI, fractionated HBI eliminates the need for the premedication or longer post-therapy

observation. Fractionated HBI proved to be safe, tolerable and effective. Five daily fractions of 3 Gy each is considered the standard HBI regimen. It also allows for an increase in the total dose when necessary.[53]

With the aim to find the fastest, most effective and economically favourable fractionated HBI regimen for symptomatic bone metastases, International Atomic Energy Agency conducted a multicentre randomise phase III trial. One-hundred-fifty-six patients with bone metastases of breast, prostate, lung and other cancer were grouped into three arms: *(1)* controls –15 Gy in 5 fractions over 5 days; *(2)* hyperfractionation – 8 Gy in 2 fractions over 1 day; and *(3)* accelerated – 12 Gy in 4 fractions over 2 days. The results indicated that for most tumour types (an exception was cancer of the prostate) two daily doses of 3 Gy delivered in 2 consecutive days were as effective as a 5-day regimen of 3 Gy-daily fractions.[51]

Radioisotopes

The radionuclide therapy for bone pain has been used for more than 30 years. Acting systemically, a targeted therapy with radioisotopes is indicated in the management of disseminated disease when the repeated local treatments would become impractical. The potential toxicity of systemic administration of radioisotopes is reduced by their relatively selective targeting of the tumour. For the efficacy of this treatment the proper selection of patients is of paramount importance.

The following radionuclides were used in the treatment of painful bone metastases: 32-P, 89-Sr, 186-Re, 188-Re, 153-Sm, 223-Ra and 117-Sn. Most studies with these agents have been conducted in prostate and breast cancer patients and the most widely used isotopes were 89-Sr and 153-Sm.[16,20,54]

Bone targeting relies upon the selective uptake and prolonged retention of radionuclide molecules at sites of the increased osteoblastic activity on the border between bone and osteoblastic metastases. Some radionuclides have natural affinity for metabolically active bone (such as 89-Sr and 223-Ra) whereas the others (153-Sm and 186-Re) form stable complexes with bone-seeking cations, such as phosphate and diphosphonate.

Strontium (89-Sr) is an element that behaves biologically like calcium. As a group II metal, strontium has a natural affinity for metabolically active bone. After the intravenous administration, 89-Sr is concentrated in bone in proportion corresponding to osteoblastic activity. Of the 89-Sr that is not concentrated in bone, the excretion is predominantly renal (about 80%) and about 20% through the gastrointestinal system. A 89-Sr therapy is recommended for the patients with moderate pain and reasonable life expectancy. Published data reported a pain relief in approximately 74% of patients. The onset of the pain relief is generally within 7-21 days post-therapy, with a mean duration of relief of about 6 months. Transient increase in bone pain (painful flare) may occur in the first 2-3 days after the treatment and is usually of mild intensity, easily controlled with analgesics. The toxicity of such treatment is limited to temporary myelosupression, which typically occurs 6 weeks after the therapy and continues during the next 6 weeks.[16,54]

Comparing the effectiveness of 89-Sr and external beam radiotherapy (local radiotherapy or HBI), no difference in the median survival (89-Sr – 33 weeks, external beam radiotherapy – 28 weeks) and in pain relief at 3 months (89-Sr – 66.1%, local radiotherapy – 65.9%, HBI – 63.3%) were observed between the three treatment modes. However, whereas the retreatment rates between 89-Sr and external beam radiotherapy were comparable, after 89-Sr treatment significantly fewer patients reported new

pain sites than after the local radiotherapy or HBI.[39] It was also reported that the addition of 89-Sr to local radiotherapy of painful bone metastases reduced the progression rate in endocrine resistant metastatic prostate cancer.[55]

Samarium (153-Sm) forms a stable complex with ethylenedinaminetetramethylene phosphonic acid (EDTMP). This phosphonate complex concentrates in the skeleton, in proportion that corresponds to osteoblastic activity. Together with beta-rays samarium emittes also gamma rays. After the intravenous administration, phosphonate complex has a rapid bone uptake and plasma renal clearance. A pain relief was observed in 62-74% of treated patients with higher overall response rates at higher doses. The response duration was about 8 weeks (range 4-35 weeks). The bone marrow suppression was generally mild and reversible, and pain flare was rare. 153-Sm is the most widely used radiopharmaceutical agent for palliation of bone pain in the United States.[16,54]

In the therapy with radionuclids two rhenium isotopes, 186-Re and 188-Re have been used. They belong to group of beta-emitters. Several initial studies reported the safety and efficacy of using rhenium isotopes. In the study of Piffanelli *et al.*[56] no differences was found between 186-Re and 89-Sr concerning the response rate which was not related to patients' age, skeletal extension of tumour, evidence of non-bony metastases, previous chemotherapy and/or external-beam radiotherapy. However, osteolytic lesions responded worse than osteoblastic or mixed ones. Haematological toxicity (mild to moderate), mainly affecting platelets, was observed in 25.5% of all treatments and in 38.9% of retreatments.

The Cochrane review of four randomised trials showed that radioisotopes might completely abolish pain over one to six months with no increase in the analgesic use; adverse effects, specifically leukocytopenia and thrombocytopenia, had also been experienced.[57] Thus palliation of bone pain with radioisotopes is indicated as a complementary therapy to other treatment modalities in context of an interdisciplinary pain management.[58] While the external beam radiotherapy remains the mainstay of pain palliation of solitary bone lesions, bone-seeking radiopharmaceuticals have a role in selective cases with multiple osseous metastases.[59]

Table 2. Commonly used indications for surgical treatment of pathologic bone fractures and impending fractures (prophylactic fixation) in patients with bone metastases

Pathologic fractures
Expected survival longer than 6 weeks
No greater benefit from nonoperative treatment
Ability to obtain internal stability
Patients condition permits operation
Early mobilization possible
Impending fractures
Metastasis in weight-bearing bones
Lytic lesions with a diameter >2-3 cm or with cortical destruction > 50%

Surgery

In the case of pathologic fractures, there are two local therapeutic options available, including radiotherapy and/or surgery. For the surgical treatment commonly used indications are also impending fractures (Table 2).[1] In selected cases, the implementation of new minimally invasive procedures (*i.e.* MR-guided focused ultrasound surgery and percutaneous polymethylmethacrylate vertebroplasty) that offer a remarkable advantage of effective and immediate pain relief with few complications, should be considered.[17,60,61]

Malignant spinal cord compression asks for the most urgent surgical intervention.

Table 3. Bisphosphonates approved for the treatment of breast cancer patients with bone metastases[3,67]

	Relative potency	Dose (mg)	Schedule	Mode of administration
Non-nitrogen				
Clodronate	1	1600	daily	oral
Single-nitrogen				
Pamidronat	20	90	every 3-4 weeks	2 hours *i.v.*
Ibandronat	857	6	every 3-4 weeks	1 hour *i.v.*
		50	daily	oral
Two nitrogens				
Zolendronic acid	16700	4	every 3-4 weeks	15 min *i.v.*

The decision on treatment modalities or combination of different therapies (surgery with postoperative radiotherapy, radiotherapy only, specific therapies according to tumour type) should be carried out on multidisciplinary setting according to the neurological, oncological, orthopedical and systemic principles.[9]

Bisphosphonates

Bisphosphonates are synthetic analogues of naturally occurring pyrophosphate compounds that inhibit calcification.[62] They bind preferentially to bone at sites of active bone metabolism and are released from the bone matrix during bone resorption. Potently they inhibit the osteoclast activity and the survival, thereby reducing the osteoclast-mediated bone resorbtion.[63] Results of *in vitro* studies have shown that bisphosphonates inhibit tumour cell adhesion and invasion of the extracellular matrix. They also induce tumour-cell apoptosis.[64,65]

Bisphosphonates are used in treatment of many disorders, such as metabolic bone disease, Paget´ disease, osteoporosis and metastatic bone disease. They have also shown the efficacy in the cancer treatment-induced bone loss.[62,66]

Bisphosphonates have emerged in recent years as a highly effective therapeutic option for the prevention of skeletal complications secondary to bone metastases. The clinical benefits of the bisphosfonate therapy have been evaluated in many clinical trials. The majority of these trials used a composite end point defined as a skeletal-related event (SRE) or bone event, which generally includes events such as pathologic fracture, radiation to bone, surgery to bone spinal cord compression and hypercalcaemia due to underlying malignancy.[3,20,67,68]

Bisphosphonates have become the current standard of care for preventing skeletal complications associated with bone metastases. There are several bisphosphonates that are used for the treatment of patients with bone metastases from breast cancer (Table 3).[67] Zoledronic acid, pamidronate, clodronate and ibandronate all have demonstrated the efficacy superior to that of placebo in patients with breast cancer.[3,69] The efficacy of zoledronic acid and pamidrinate was compared in randomized fashion and the former was shown to be significantly more effective at reducing the risk of an SRE.[3,70]

Zoledronic acid and ibandronate were also shown to exert synergistic antitumour activity when combined with various specific anticancer treatments such as chemotherapy, hormone therapy, radiotherapy or monoclonal antibodies.[71-74] However, due to potential nephrotoxic effect of *i.v.* bisphosfonates, chemotherapy noxious to the kidneys should not be administered on the same day as bisphosphonates.[66]

Conclusions

Relieving bone pain in cancer patients is integral and crucial part of the comprehensive cancer management. Radiotherapy is an important mode for the local and systemic pain relief. It effectively decreases morbidity caused by painful bone metastases, resulting on substantial improvement of the quality of patient's life. No matter what kind of treatment modality or their combinations is planned to be applied, it should be tailored according to the patient's clinical condition and life expectancy.

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research article

Budd-Chiari syndrome associated with liver hydatid disease: retrospective evaluation of color Doppler US findings with emphasis on intrahepatic venous collateralization

Cengiz Yilmaz[1], Nazif Erkan[2], Muhammet Arslan[1], Yusuf Yildirim[2], Sena Kalaycioglu[3]

[1]Department of Radiology,
[2]Department of General Surgery, Izmir Bozyaka Training and Research Hospital, Bozyaka,
[3]Department of Radiology, Sifa Hospital, Basmane, Izmir, Turkey

Background. *The purpose of this retrospective study is to evaluate the color Doppler US (CDUS) findings of Budd-Chiari Syndrome (BCS) associated with hydatid disease of the liver (HDL) with a special emphasis on the intrahepatic venous collateralisation.*

Methods. *Digitally stored CDUS videoclips or videotape records of the liver of 13 patients with HDL and BCS were retrospectively reviewed. A special emphasis was placed on intrahepatic venous collaterals compatible with BCS.*

Results. *During the retrospective analysis of the sonographic data, at least one type of intrahepatic venous collateral typical for BCS was detected in all patients. CDUS revealed 5 different types of intrahepatic venous collaterals including subcapsular veins, comma-shaped veins which sometimes resemble hockey-stick, spider-web collaterals, fragmented veins and linear veins distributed in a non-anatomical fashion. The most frequently encountered collaterals at CDUS were comma-shaped veins, seen in 12 of 13 (92.3%) patients. In addition, at least 2 different types of intrahepatic collaterals were found in 8 of 13 (61.5%) patients. In two patients, venous collaterals were not seen on gray-scale sonography, but they were apparent at CDUS.*

Conclusions. *BCS secondary to HDL may come as an unexpected finding during sonography. Familiarity with the typical sonographic appearances of the intrahepatic venous collaterals associated with BCS may enable the correct diagnosis and the prompt further treatment. We recommend CDUS to be performed in every patient with HDL regardless of the clinical presentation.*

Key words: Budd-Chiari syndrome; liver hydatid disease; color Doppler sonography

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Correspondence to: Dr. Cengiz Yilmaz, Izmir Bozyaka Training and Research Hospital, Department of Radiology, Saim Cikrikci Street, 35360, Bozyaka, İzmir, Turkey. Phone: +90 532 475 80 94; Fax: +90 232 261 44 44; E-mail: cengizyilmaz66@yahoo.com

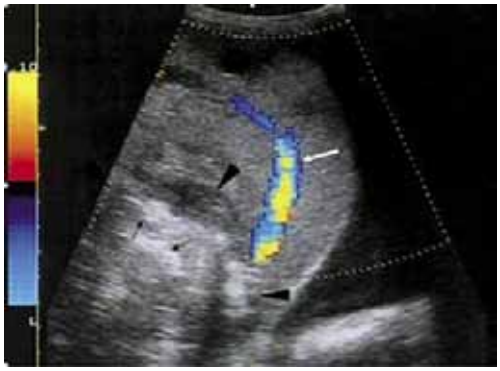

Figure 1A. A 37-year-old woman with HDL and BCS presented with right upper abdominal pain and fever. Sagittal color Doppler sonogram reveals a heterogeneous mass (arrowheads) including hyperechoic linear, serpentine structures (black arrows) representing degenerated and collapsed membranes. Also noted is a large subcapsular collateral vein (white arrow) which was shown to drain into the suprahepatic inferior vena cava at real time US.

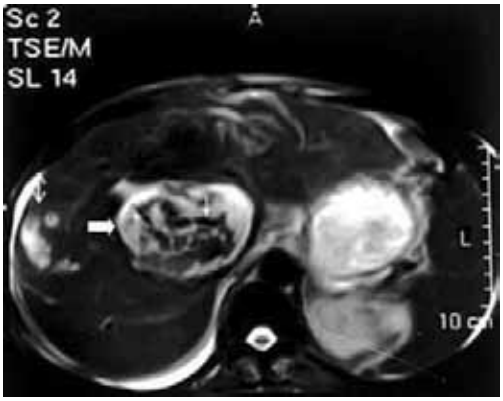

Figure 1B. A 37-year-old woman with HDL and BCS presented with right upper abdominal pain and fever. TransverseT2-weighted MR image shows hydatid cyst (thick arrow) with multiple hypointense linear and band like structures (thin arrows) representing detached and degenerated membranes. Also noted is focal disruption of the hypointense band at the anterior aspect of the hydatid cyst, suggesting rupture.

Introduction

Budd-Chiari Syndrome (BCS) develops secondary to hepatic venous obstruction or interruption of the suprahepatic vena cava inferior (IVC).[1,2] In the western world, the most common causes are prothombotic disorders like polycythaemia vera, whereas membranous obstruction is the leading cause in Asia.[3,4] Hydatid disease of the liver (HDL) is a rare cause of BCS and is primarily encountered where the disease is endemic.[5,6] The clinical presentation depends on the extent of the obstructive process, how quickly it develops and the degree of the intrahepatic collateralisation.[7] The diagnosis of BCS is often missed unless its possibility has been kept in mind.[8]

Altough the association of BCS and HDL has been previously reported, most of these studies are either case reports or clinical studies without any significant imaging evidence.[9-13] To the best of our knowledge, our study is the first in which this association is demonstrated at US in a relatively high number of patients. The aim of this retrospective study is to report a group of patients who developed BCS secondary to HDL, with the special emphasis on the sonographic appearances of typical intrahepatic venous collaterals that aid in the correct diagnosis.

Patients and methods

Thirteen patients (8 women, 5 men, age range 16-71 years, mean age 38 years) who were diagnosed with HDL and BCS at US within an eight-year period were included in this study. Videotape records or videoclips stored in the hard drive of the US scanner including both gray-scale and color Doppler examinations were retrospectively evaluated by two radiologists with at least 10 years experience in abdominal CDUS. Both radiologists evaluated the examinations independently. In case of discordance, interpretations were performed by the consensus review.

Color Doppler examinations were evaluated for the presence of the following intrahepatic venous collaterals which are

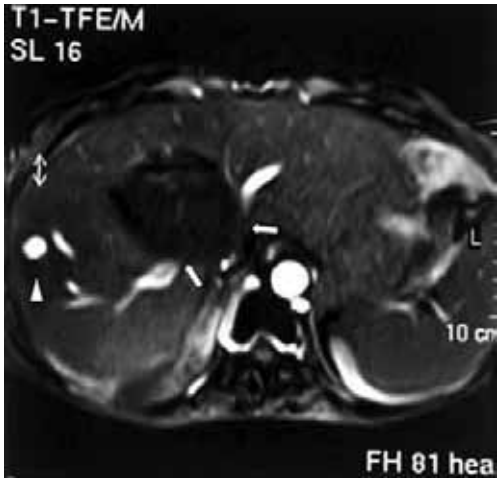

Figure 1C. A 37-year-old woman with HDL and BCS presented with right upper abdominal pain and fever. Transverse T1-weighted contrast-enhanced MR image also reveals the large subcapsular collateral (arrowhead). Both the left and right hepatic veins (arrows) are compressed at the hepatic venous confluence. At surgery, an infected hydatid cyst with intrahepatic rupture was found.

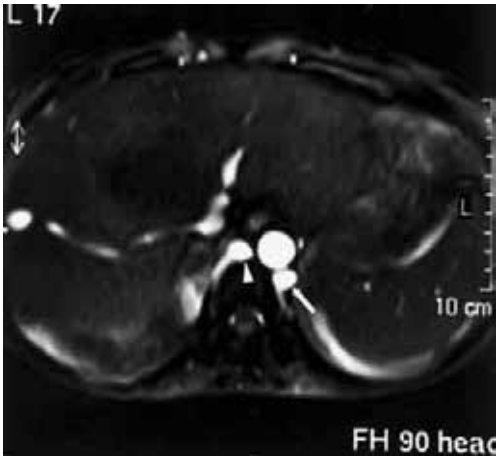

Figure 1D. A 37-year-old woman with HDL and BCS presented with right upper abdominal pain and fever. TransverseT1-weighted contrast-enhanced MR image at a slightly different level than Figure1-C demonstrates the dilated azygos (arrowhead) and hemiazygos veins (arrow) which act as extrahepatic collaterals to provide drainage for obstructed hepatic venous flow. These collaterals could not be demonstrated at US.

considered almost typical for BCS: (1) subcapsular collateral veins, (2) comma-shaped veno-venous collateral veins, (3) fragmented veins, (4) spider-web veins and (5) linear veins arranged in a non-anatomical distribution.[7,14,15] In addition, the localization and relationship of the hydatid cyst with regard to the hepatic veins and/or suprahepatic IVC were also evaluated. HDL was sonographically classified according to an international consensus classification proposed by WHO.[16] According to this classification, the cystic lesion (CL) represents an unilocular cyst with no visible cyst wall, type1 cystic echinococcosis (CE)1 represents unilocular cysts with visible cyst wall, type CE2 represents multivesicular cysts with daughter cysts, type CE3 represents cysts with floating membranes or complex hydatid cysts with a semisolid appearance, type CE 4 represents hydatid cysts with a heterogeneous hypoechoic appearance and finally type CE 5 represents hydatid cysts with thick calcified walls. Because of their nonspecific US appearances, CL's were not included in this present study. The mean diameter of the hydatid cysts as measured at US was 12.2 cm (range, 6-21 cm), all located at the hepatic dome. Based on WHO classification, one of 13 of our patients (7.7%) had type CE1, six (46.2%) patients had type CE2, two (15.4%) patients had type CE3, three patients (23.1%) had type CE4 and the remaining patient had type CE5.

Gray-scale and CDUS examinations were performed either with a Toshiba SSA 270 A (Tokyo, Japan) unit or GE Healthcare (Milwaukee, WI) LOGIQ 9 machine equipped with 3.75 MHz and 5-12 MHz broadband transducers, respectively.

All MRI studies were performed on a 1.5T MRI unit (Gyroscan Intera, Philips Medical Systems, Netherlands). Nonenhanced T1 and T2 -weighted images and dynamic contrast-enhanced MR images of the liver were obtained in 10 patients.

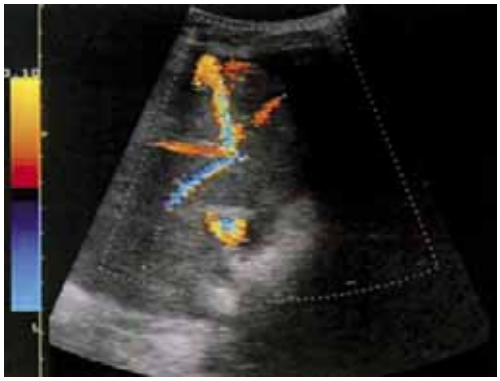

Figure 2A. A 43-year-old man with BCS and HDL presented with nonspecific right upper abdominal pain. Transverse color Doppler sonogram obtained in right intercostal plane and showed collateral veins suggesting BCS. Poor patient cooperation and extensive gasseous distention hampered both the evaluation of the major hepatic veins and the hydatid cyst.

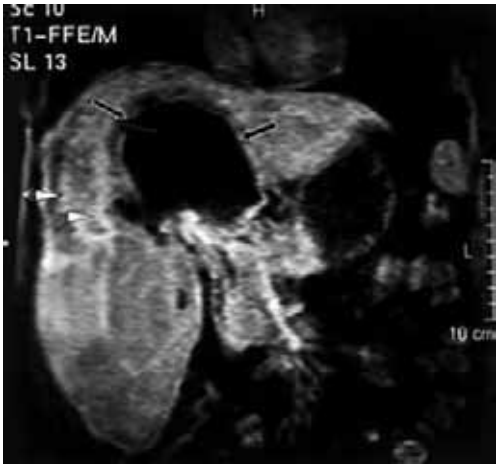

Figure 2B. A 43-year-old man with BCS and HDL presented with nonspecific right upper abdominal pain Coronal T-1 weighted contrast-enhanced MR image reveals both the hydatid cyst (arrows) and collateral veins (arrowheads).

MR images were evaluated for (1) the localization and relationship between the hydatid cyst and hepatic veins and/or suprahepatic IVC, (2) patency of the major hepatic veins and/or suprahepatic IVC and (3) presence of intrahepatic and extrahepatic collateral veins.

The reason for the referral was to rule out BCS in 10 patients. Clinical findings included hepatomegaly (9 patients) splenomegaly (3 patients), lower extremity swelling (2 patients), ascites (8 patients), and superficial abdominal collaterals (4 patients). Oesophageal varices were evident endoscopically in 4 patients. In the remaining 3 patients, the clinical presentation was nonspecific including abdominal fullness, right upper abdominal pain and fatique.

Results

During the retrospective analysis of sonographic data, at least one type of intrahepatic venous collateral typical for BCS was detected in all of our 13 patients with HDL and BCS. At CDUS, five different types of intrahepatic venous collaterals including subcapsular veins (Figure 1a), comma -shaped veins which sometimes resemble a hockey-stick (Figures 2c, 2d), spider-web collaterals (Figure 3a), fragmented veins (Figure 3b) and linear veins arranged in a non-anatomical distribution (Figures 2a, 4b) were identified. The most frequently encountered collaterals at CDUS were comma-shaped veins which were seen in 12 of 13 (92.3%) patients. Subcapsular collaterals were detected in 8 patients, linear veins arranged in a non-anatomical distribution were seen in 5 patients, spider web collaterals were encountered in 4 patients and fragmented veins were seen in 4 patients. In addition, at least 2 different types of intrahepatic collaterals were found in 8 of 13 (61.5%) of our patients. In two patients, venous collaterals were not seen on gray-scale sonography but they were readily apparent at CDUS (Figure 4). All of the sonographically detected collateral veins demonstrated a monophasic-flat flow at Duplex Doppler US. At gray-scale US, a nonspecific heterogenous hepatic echo-

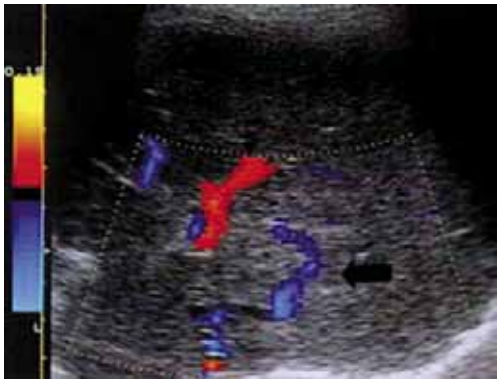

Figure 2C. A 43-year-old man with BCS and HDL presented with nonspecific right upper abdominal pain. Oblique subcostal color Doppler image depicts hockey-stick collateral (arrow) which drained direcly into the IVC.

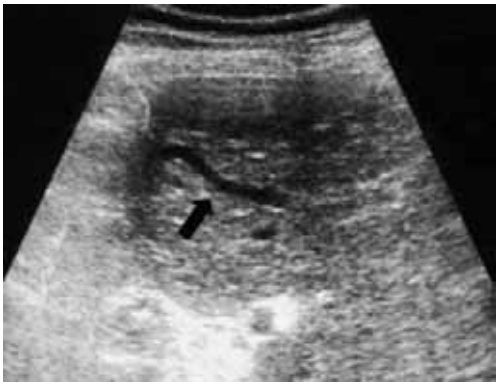

Figure 2D. A 43-year-old man with BCS and HDL presented with nonspecific right upper abdominal pain Transverse gray-scale sonogram obtained in the same patient reveals typical comma-shaped collateral (arrow) in a subcapsular location. At Duplex Doppler imaging, this vein demontrated monophasic flow (not shown). Comma-shaped collaterals are highly suggesitve, if not diagnostic of BCS.

pattern was observed in 8 patients. In 2 patients US showed a sharp demarcation between the anterior and posterior parts of the liver. The anterior part of the liver demonstrated diffuse hypoechogenicity with multipl coma-shaped venous collaterals, whereas the posterior part of the liver showed diffuse hyperechogenicity with no vascularisation at CDUS (Figure 5).

Only 3 different types of intrahepatic intrahepatic venous collaterals were visible at MR imaging. Subcapsular colllaterals were the most frequently detected collaterals at contrast – enhanced MR imaging and they were seen in 4 patients. Comma-shaped collaterals were detected in 3 patients, whereas, linear veins arranged in a non-anatomical distribution were observed in 2 patients. The spider -web collateral veins and fragmented collateral veins detected at CDS were not visible at MR imaging. No intrahepatic venous collateral could be identified in 4 of 10 patients who underwent MR imaging. On the other hand, MR imaging showed stenosis or severe compression of at least one major intrahepatic vein and / or suprahepatic IVC in all 10 patients for whom MR imaging was available (Figure 1c). At CDUS, however, stenosis or severe compression of the major hepatic veins or suprahepatic veins could be demonstrated in 6 of 13 (46.2%) patients.

Extrahepatic collaterals were seen in 5 of 10 (50%) patients (Figure 1d) for whom MR imaging was available. No extrahepatic collaterals were identified at CDUS. In addition, neither CDUS nor MR imaging revealed portovenous collaterals. The portal vein was dilated (diameter more than 13 mm) in 5 patients. Portal venous thrombosis was not observed in any patient.

Discussion

BCS secondary to HDL can occur if large hydatid cysts in the hepatic parenchyma compress the hepatic veins. To produce BCS, cysts have to be very large and lie in an appropriate position. Endoveinitis may also be a contributing factor to the development of BCS in HDL, especially in advanced stages.

As reported in a previous study, asymptomatic Budd-Chiari syndrome is not rare

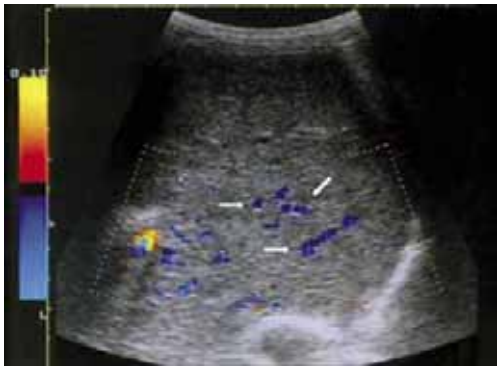

Figure 3A. A 44-year-old woman with BCS and HDL presented with upper abdominal pain. A unilocular hydatid cyst located at the hepatic dome was seen at gray-scale US (not shown). Oblique subcostal color Doppler image reveals spider-web collaterals (arrows).

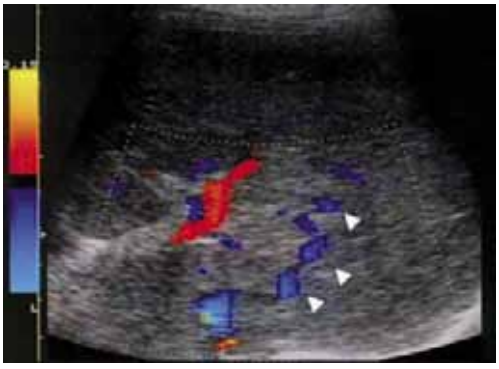

Figure 3B. A 44-year-old woman with BCS and HDL presented with upper abdominal pain. A unilocular hydatid cyst located at the hepatic dome was seen at gray-scale US (not shown). Color Doppler sonogram shows fragmented collateral veins (arrowheads). Both spider-web and fragmented collateral veins are almost diagnostic of BCS and may not be demonstrated at MR imaging, as it was in our case.

and accounts for 15 to 20% of cases.[17] Asymptomatic Budd-Chiari syndrome is associated with the spontaneous development of large intrahepatic and portosystemic collaterals.

Diagnosis of BCS based on direct US criteria may be difficult in patients even when the diagnosis is suspected clinically. Diagnostic difficulties at US include an inadequate evaluation of the major hepatic veins due to obesity, extensive bowel gas, cirrhosis, ascites and hepatomegaly. Intrahepatic venous collaterals are considered the most sensitive feature for the diagnosis of BCS, found in more than 80% of cases. Thus, familiarity with the sonographic appearances of these collaterals may aid in the correct diagnosis when the direct evaluation of the major hepatic veins is problematic at CDUS. Intrahepatic venous collaterals almost diagnostic of BCS were seen in all of our 13 patients at CDUS.[7,14,15]

In 2 of our patients who presented with the typical triad of BCS, US revealed an avascular, hyperechoic region in the peripheral, posterior aspect of the right hepatic lobe with a sharp demarcation zone (Figure 5). We believe that this appearance is analogous to the previously reported CT appearance of BCS and is related to congestion, edema and ischemia.[14]

Intrahepatic collateral veins resembling those seen in BCS have also been reported in Rendu-Osler-Weber syndrome, diaphragmatic hernia and congestive heart failure. However, in these clinical conditions collateral veins almost always show a pulsatile flow, whereas collateral veins in BCS typically demonstrate a monophasic flow at Duplex US.[18]

Extrahepatic collaterals were apparent in 5 patients at MR imaging (Figure 1d). None of these extrahepatic collaterals were visible at gray-scale US and MR imaging MRI seemed to be superior to US in this context.

HDL may not be a rare cause of BCS, especially where hydatid disease is endemic. Indeed, in a recent study which was done in an endemic area for hydatid disease, HDL was the second most frequent cause of BCS and constituted 8% percent of all patients with BCS.[4]

Our study has some limitations. Due to the limited number of patients with BCS and HDL, the statistical analysis was not performed. Nevertheless, US seemed to

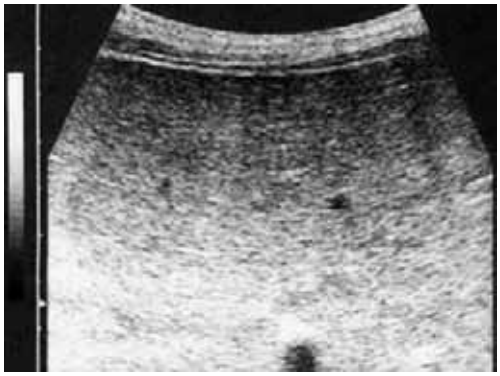

Figure 4A. Transverse magnified gray -scale sonogram of a 47-year-old man with BCS and HDL. The parenchymal echopattern appears heterogeneous. No apparent collateral vessel can be identified.

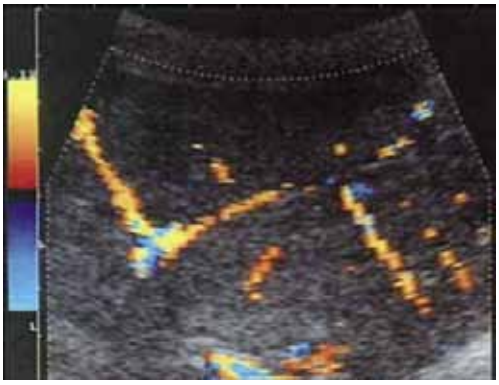

Figure 4B. Transverse magnified color Doppler sonogram of a 47-year-old man with BCS and HDL. At color Doppler imaging multipl intrahepatic collateral veins are easily seen.

be superior to MRI in the demonstration of intrahepatic collaterals, whereas, MRI prevailed US in the demonstration of major hepatic venous or IVC involvement. Another limitation of our study is that the caudate lobe vein was not evaluated. We believe that the caudate lobe vein should be assessed during focused real-time examinations and retrospective evaluations may not be reliable to confirm or exclude dilatation of the caudate lobe vein.

In conclusion, our study shows that BCS secondary to HDL may not be exceptionally rare and may come as an unexpected finding during sonography. Familiarity with the typical sonographic appearances of the intrahepatic venous collaterals associated with BCS may enable the correct diagnosis and the prompt further treatment. We recommend CDUS to be performed in every patient with HDL regardless of the clinical presentation.

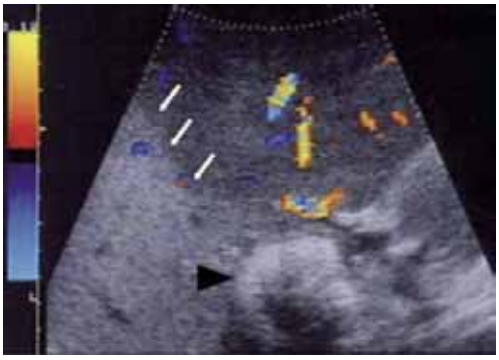

Figure 5. A 35-year-old woman presented with severe right upper abdominal pain, hepatomegaly and ascites. Color Doppler image reveals a sharp demarcation zone between the anterior and posterior parts of the right liver lobe (arrows). Also noted is a totally calcified hydatid cyst (arrowhead). The anterior part of the liver is hypoechoic and contains multipl comma–shaped venous collaterals.The posterior portion of the right liver lobe demonstrates increased echogenicity, possibly secondary to hepatic congestion and/or edema.

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case reports

Migration of Enterprise stent in treatment of intracranial aneurysms: a report of two cases

Goran Pavlisa[1], David Ozretic[1], Marko Rados[1], Gordana Pavlisa[2]

[1] *Clinical Institute of Diagnostic and Interventional Radiology, University Hospital Center Zagreb, Zagreb School of Medicine;* [2] *Special Hospital for Pulmonary Diseases, Zagreb, Croatia*

Background. *We present two patients with acutely ruptured complex aneurysms of the internal carotid artery, arising at the origin of the posterior communicating artery (PComA).*
Case reports. *The aneurysms in both patients had a wide neck and the closed-cell stent (Enterprise) was delivered to assist in aneurysm coiling. In both patients an inadvertent migration of stent occurred, without periprocedural complications. Aneurysms were successfully embolized by endovascular coils.*
Conclusions. *These cases highlight the flexibility of the stent, as well as the likelihood of stent migration in the setting of immediate coiling after the placement of stent, or in adverse anatomic relations.*

Key words: intracranial stent; complex aneurysm; stent migration

Introduction

In patients with large or giant intracranial aneurysms, with arterial branches originating from the aneurysm, or when wide neck of the aneurysm circumferentially involves the parent artery, the treatment is often difficult. Endovascular treatment options include the use of three-dimensional coils, stent placement, balloon remodelling[1-3], the use of liquid embolics[4], multiple microcatheters[5] and combinations of these approaches.[6-9] We present two patients with acutely ruptured complex aneurysms of the origin of the posterior communicating artery (PComA). The patients were treated by stent-assisted coiling, using Enterprise stent, which migrated after the initial successful deployment. The stent migration occurred after a very moderate negotiation of the microcatheter through the struts of the stent in the first patient, and without any manipulation in the second patient.

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Correspondence to: Dr. Goran Pavlisa, Clinical Institute of Diagnostic and Interventional Radiology, University Hospital Center Zagreb, Kispaticeva 12, Zagreb, Croatia. Phone: +385 1 2388118; Fax: +385 1 2388250; E-mail: gpavlisa@net.amis.hr

Case reports

Patient 1

Clinical details

A 53-year-old female patient was admitted to hospital after suffering sudden headache accompanied with nausea, vomiting, and diplopiae. Head computerized tomography

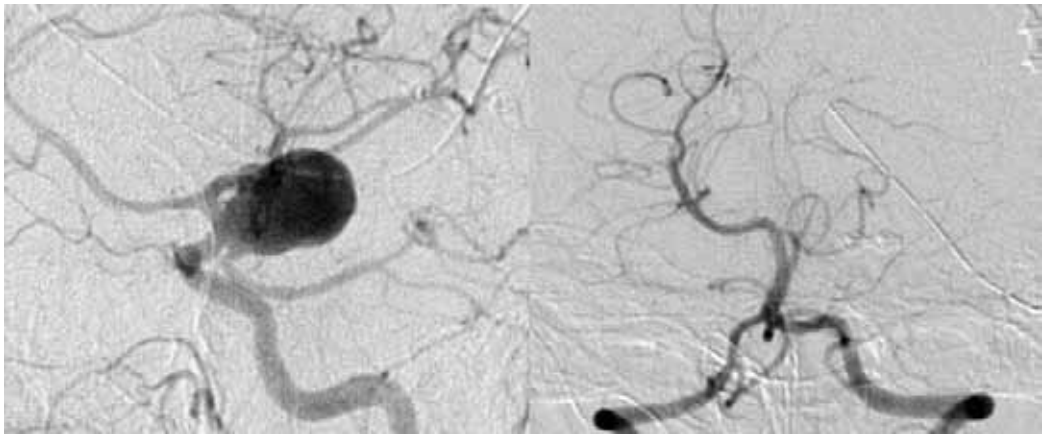

Figure 1. Large aneurysm of the posterior communicating artery origin (*left*). The foetal origin of the left posterior cerebral artery is shown by the left vertebral artery angiogram (*right*).

(CT) scan revealed diffuse subarachnoid haemorrhage (SAH) with intraventricular extension and brain oedema. CT angiography displayed a large aneurysm of the origin of posterior communicating artery (PComA), with mural thrombus and a wide neck. Left PComA was of a foetal type with the complete absence of P1 segment of the left posterior cerebral artery (PCA). The patient was referred to the open neurosurgical treatment, however, the surgical reconstruction of the neck and aneurysm occlusion could not have been performed due to a high risk of PComA occlusion and ipsilateral PCA infarction.

The patient was transferred to our institution for the endovascular treatment on the following day. The control CT showed no significant changes compared to the initial scan, with no signs of secondary ischemic changes or hydrocephalus and she underwent the immediate endovascular treatment.

Endovascular treatment

Diagnostic four-vessel angiography was performed through the right femoral approach and 6 French (6F) introducer sheath, confirming the aneurysm, with foetal left PCA. The circulating lumen of the aneurysm was large, 19 x 13 x 15 mm in diameter, with a 6 mm-wide neck (Figure 1).

A 6F guiding catheter (Multipurpose, Boston Scientific Neurovascular, Fremont, CA, USA) was placed in C1 segment of the left ICA, and the aneurysm was catheterized using Excel 0.014 inch microcatheter and Synchro 0.014 microguidewire (Boston Scientific, Fremont, CA, USA) for initial coiling with bare platinum Guglielmi detachable coils (GDCs). Eight coils were placed in the aneurysm dome, with a total length of 220 cm. At that time, due to the risk of coil protrusion in the ICA and PComA, a microcatheter was exchanged for a Prowler select plus 21 microcatheter for the placement of closed-cell stent (Enterprise, Cordis Neurovascular - Johnson & Johnson, Miami Lakes, FL, USA). The stent, sized 4.5 mm x 22 mm, was placed with a proximal part in cavernous ICA and distal part in M1 segment of the left medial cerebral artery, with the intention of narrowing of the aneurysm neck. Prowler microcatheter was then exchanged for Excelsior 10 microcatheter (Boston Scientific, Fremont, CA, USA) for the purpose of aneurysm coiling. In the attempts to pass the microcatheter through the struts of the stent, due to the angle of

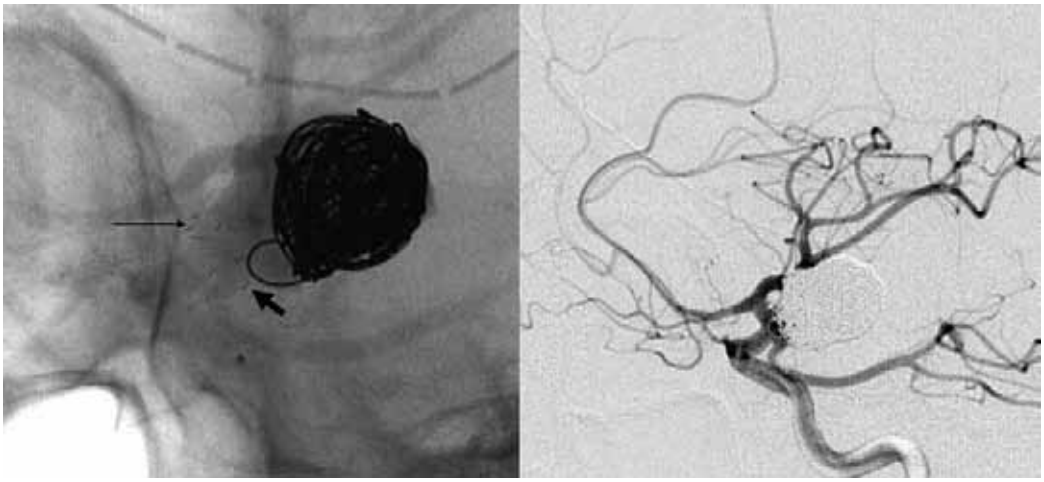

Figure 2. Radiopaque stent markers are positioned in both parts of the neck of the aneurysm, covering the neck at the internal carotid artery (*thin arrow*) and at the origin of posterior communicating artery (*thick arrow*). Near-total occlusion of the aneurysm with protrusion of one coil loop in the ICA by the side of the stent, with patent internal carotid artery and posterior communicating artery.

the ICA at the origin of the aneurysm neck, the stent was mobilised to a more proximal position, with the distal end in C7 segment of the ICA and the proximal end in the origin of PComA from the aneurysm (Figure 2). This stable position of the stent secured both ICA and PComA for the further coil embolization, with 15 GDC coils, with a total length of packed coils at the end of the procedure of 540 cm.

During coiling, an intravenous bolus of 7 mg of Integrilin has been administered at the time when the aneurysm was estimated to be secured from bleeding. The aneurysm was near-totally occluded, with a minimal neck remnant, and a slight coil loop protrusion in the ICA. PComA was patent with a normal flow in the left PCA at the end of the procedure.

After the procedure, a standard antiaggregation therapy was initiated, with aspirin 100 mg daily, permanently, and clopidogrel 75 mg daily, during 4 weeks. During the post-embolization period, the patient gradually recovered, and was discharged from the hospital to a rehabilitation centre with a moderate cognitive dysfunction.

Patient 2

Clinical details

A 54-year-old female patient was referred to the endovascular treatment of an acutely ruptured large aneurysm of PComA origin. Before the treatment, the patient was in Hunt and Hess grade II.

Endovascular treatment

At four-vessel angiography the aneurysm was irregular in shape, 14 x 8 mm in diameter, with a 5 mm-wide neck. Initial coiling attempts were unsuccessful because of a coil loop protrusion in ICA, and the Enterprise stent, 4.5 mm x 22 mm, was deployed across the aneurysm neck. However, during the first control angiogram before further microcatheter manipulation, the proximal part of the stent migrated to the aneurysm neck, while the distal remained in the initial position in M1 segment of the middle cerebral artery (Figure 3). Nevertheless, this stent position enabled successful coiling, and the aneurysm was embolized with 18 coils, with a minimal neck remnant. The post-procedur-

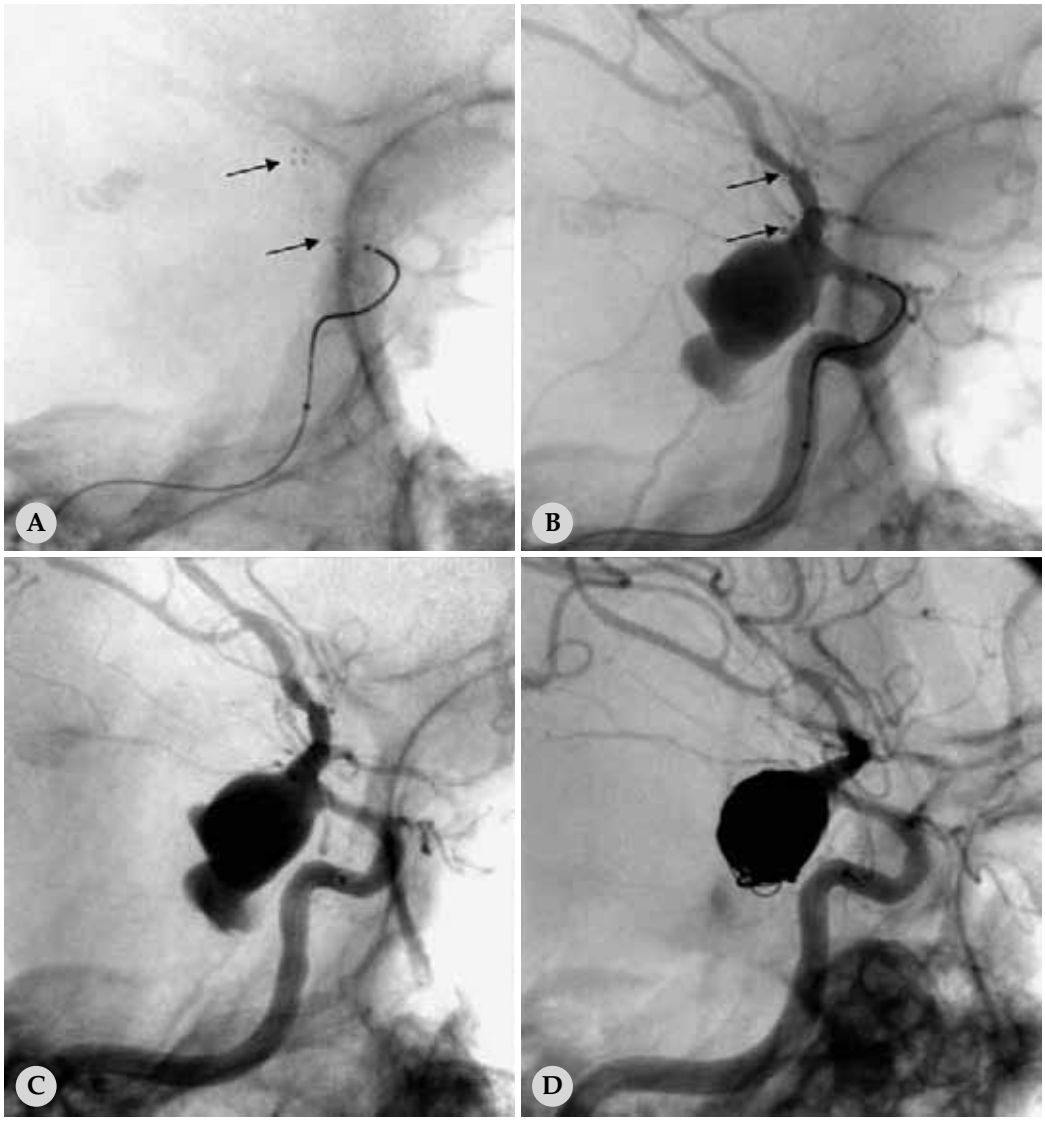

Figure 3. A: Arrows indicate proximal and distal markers of a deployed stent. B: Position of the markers after stent migration shown by arrows. Large irregular PComA aneurysm with a wide neck. C: Microcatheter in the aneurysm lumen. D: Embolized aneurysm at the end of the session.

al course was uneventful, and the patient completely recovered.

This report is written in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Both patients gave an informed consent prior to the inclusion of the data in the report. Details that might have disclosed the identity of the subject under study have been omitted.

Discussion

Self-expandable stents have increasingly been used in the treatment of various

vascular pathology.[10] The reconstruction of the parent artery at the aneurysm neck is often performed using intracranial stents, with a variety of materials, including open-cell, closed-cell stents or covered stents.[11,12] Different approaches have been described, as stenting before or after coiling[13,14], or in combination with balloon remodelling[1,3,15], Y configuration of stents[16] and stenting across the circle of Willis.[17]

In the first presented patient, the angle between C7 segment of the ICA and the origin of the PComA, through the neck of the aneurysm was acute, not allowing the stent to be positioned from ICA to PComA in a manner that would secure both arteries and allow the coil embolization. These patho-anatomic relations also precluded balloon remodelling. We decided to place a stent in the ICA across the aneurysm neck, thus securing the ICA and we expected that the PComA origin would be at least partly secured by the narrowed neck due to the stent. The aneurysm embolization was planned to be subtotal, to leave the origin of the PComA patent. Another option was to try to place a stent through the right ICA, via anterior communicating artery (AComA), this way placing one end of the stent in PComA, and another in left ICA. However, this option seemed complicated and not likely to succeed, due to the tortuous path through the A1 segment of the right anterior cerebral artery and AComA. The closed cell stent was initially placed in the left ICA; however, it inadvertently migrated in a much more favourable position, securing both ICA and PComA.

In the second patient, anatomic relations at the aneurysm neck were rather favourable for the stent deployment, which was technically simple. The stent migrated before any further manipulation of microcatheter, we presume because the proximal part of the stent was not completely open after the microcatheter (Prowler select plus 21) withdrawal.

These cases highlight the flexibility of this stent system, without the fracture of the stent, with no angiographic or clinical signs of lesion of arterial intimal layer during the migration of the stent. There were no signs of vasospasm, dissection or thrombosis. No antiaggregation or anticoagulation therapy was administered prior to the stent placement, or even immediately after its migration, since the procedure was performed in the setting of acute SAH, and the antiaggregation therapy was administered only after the aneurysms were mostly embolized by coils. These positions of the stents allowed for almost complete coil occlusion of the aneurysms.

The use of closed-cell intracranial stents, even in patients with large and anatomically complex aneurysms as described, seems a safe and effective treatment option. The complications are mostly related to the thrombogenicity of the stent, as well as the stent migration and malposition[18], and in-stent stenosis has also been reported.[19] The timing of the stent placement in relation to coiling may be critical, since the stent migration is possible, especially in angled positions, even with a low crossing-profile of the microcatheter used to pass through the struts of the stent. The previously described variations in stent timing may indicate that it would be ideal if coiling of the aneurysm could be done before stenting, with or without the need for balloon remodelling.[14] The stent placement could then be performed at the end of the procedure for the purpose of blood flow redirection and neck healing.[6] However, if balloon remodelling is necessary, this makes the procedure more complicated, not without the higher risk of thrombotic complications.

Although the open neurosurgical approach was not successful in the first patient, there is a potential for surgical techniques and dedicated materials in solving this type of problem. Parent artery sacrifice with the creation of high-flow bypass may offer the treatment to patients with aneurysms which are not accessible to endovascular techniques[20], while tangential clipping and aneurysm wrapping may be used in the treatment of dissecting aneurysms[7], however, such techniques are not widely available in many centres. Other endovascular techniques, such as stenting across the Circle of Willis[17], balloon neck remodelling[2] or catheter-assisted GDC embolisation[21,22] may also be used in the treatment of complex aneurysms, depending on the tortuousity of path through the Circle of Willis, or the possibility of adequate positioning of the balloon or assisting microcatheter.

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case report

Abscess of C1/C2 cervical vertebrae – errors in diagnosis and therapy

Milan Stanković[1], Dušan Marić[2], Miroslav Ilić[3], Igor Veselinović[4], Srdjan Ninković[1], Svetozar Sečen[5]

[1]Clinic of Orthopedics, Clinical Center Vojvodina, [2]Clinic for Pediatric Surgery Insitute for Child and Mothers Health Vojvodina, [3]Clinic for Maxillofacial Surgery, Clinical Center Vojvodina, [4]Institute for Forensic Medicine, Clinical Center Vojvodina, [5]Clinic for Abdominal and Transplantation Surgery, Clinical Center Vojvodina, Novi Sad, Serbia

Background. *Nonspecific upper cervical spine vertebra osteomyelitis is very rare. It is caused most often by contiguous spread from an adjacent focus of infection and rarely by haematogenous dissemination from an extraspinal one. We present a rare case of Coagulase-negative Stahylococcus spp cervical vertebra osteomyelitis, where the clinical presentation of the disease is often atypical.*

Case report. *We analysed the case of 57-year-old female, where we found the diagnostic error in identification of the atlas subluxation on the radiograph and neglected laboratory findings indicating the urinary infection. These led to the disease progression and occurrence of neurological sympthomatology, presented with tetraparesis. A prompt surgery in two steps was planned: the urgent surgical anterior decompression and then the occipitocervical fixation, but the patient died after the first surgical session.*

Conclusions. *The early recognition of symptoms and a prompt diagnosis are always essential for the onset of the accurate therapy. An additional destabilization of the affected segment done by the surgical decompression in the fist step without the adequate stabilization may lead, as shown here, to a sudden fatal outcome.*

Key words: vertebral ostemyelitis; magnetic resonance imaging; surgery

Introduction

Nonspecific vertebral osteomyelitis accounts for 3-4% of all spinal infections. The cervical spine is affected in 3-10% cases, while the epidural abscess in this region is estimated to occur in approximately 1/100.000 people.[1] The infection is developed by haematogenous dissemination from an extraspinal focus or direct inoculation of a causative agent into the venous plexus around odontoid processus during the intervention in the pharynx.

In most cases the causative pathogen is *Staphylococcus aureus*. Despite the fact that the clinical presentation is often atypical, which leads to a delayed diagnosis, an early diagnosis of the disease is essential for the

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Correspondence to: Dušan Marić, MD, Clinic for Pediatric Surgery, Institute for Child and Mothers Health Vojvodina, Novi Sad, Serbija. Phone: +381 63 809 89 66; E mail: dmaric@sbb.co.yu

adequate treatment.[2] The erroneous interpretation of radiographs additionally delays a proper diagnosis and commencement of the treatment. A two-step surgical strategy can lead, as shown in here, to the risk of developing an additional destabilization of the vertebral segment. The risk is even greater if the decompression is not accompanied by the adequate fixation.

Pyelonephritis as a source of haematogenous dissemination of the pathogen, to our knowledge, has not been specifically reported. Long time wasted, till a proper diagnosis was made due to serious overlooks in reading radiographs and subsequent inadequate treatment, rare cause of the disease, and an unexpected outcome despite the favourable clinical course, make this case interesting.

Case report

A 57-year-old female admitted to the Neurology Clinic with progressive weakness and numbness in extremities, more on the right side. On the clinical examination, she complained of pain in the neck and head, behind the ears and in the region of temporomandibular joints, and hard swallowing. The discomfort lasted for about a year, while progressive weakness in her extremities appeared one week before her admittance. The symptoms began after a cold, left undiagnosed and untreated, which had stopped spontaneously. She did not complain of urinary system discomfort. With "the neck-pain syndrome" diagnosis, she was treated by a physiatrist for several months, without success, X-ray films of the cervical spine taken as outpatient clinic six months before her admittance revealed atlantoaxial subluxation (Figure 1). Duplex US – carotid, TCD-VB – normal, electromymiography made three months before admittance indicated mild neurogenic lesion of the C7 and C8 myotome, bilateral Carpal Tunnel Syndrome, and thoracic outlet syndrome to the left.

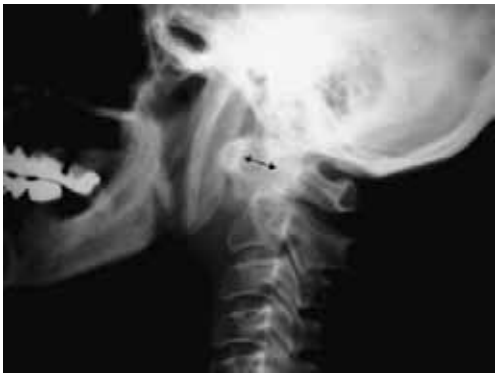

Figure 1. Lateral radiograph of the cervical spine taken one month after the onset of symptoms. Anterior atlantodental interval of 9 mm indicates anterior atlas subluxation.

The clinical examination revealed that the patient is subfebrile with anterior, posterior cervical, submandibular and suboccipital lymphadenopathy. A mild torticollis to the right with a spasm of the paravertebral musculature, more pronounced on the right was observed as well as a mild protrusion of the head in relation to the trunk. Neurological findings showed somewhat lower left angle of her lips, and tetraparesis of spastic type affecting extremities, also more pronounced on the right side. Three days before the admittance, the patient was not able to walk alone. Relevant laboratory findings were: RBC: 4.75 x 10^{12}/L, WBC: 9.0 x 10^{9}/L, Ht: 40.1, Hgb: 13.4 g/L, SR: 50/76, CRPN: 59.8 mg/L, Fibrinogen: 4.77 g/L, Glucose: 6.21 mmol/L. T3 and T4 – normal, Urine: slightly turbid, yellow in colour, pH = 6.0, relative density: 1025. Urine sediment: elongated erythrocyte 4-6, leukocytes 2-3, epithelium cells 2-3, uric acid crystals 3-4.

During the hospitalization: contrast enhanced CT of the brain and chest X-ray was normal. MRI (magnetic resonance imaging) of the cervical spine showed an extensive soft tissue infiltration at the C1-2 level with

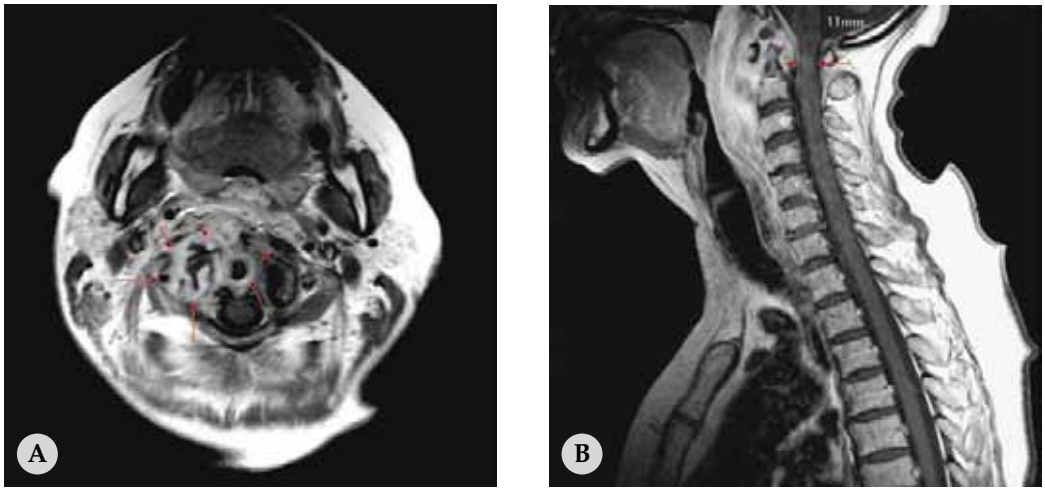

Figure 2. MRI images of the cervical spine:
A. Axial TI-weighted image of the cervical spine at the level of C1. Formed abscess infiltration, partial erosion of the right atlantoaxial joint, surrounded dens, and abscess penetration into the epidural space.
B. Sagittal Tl-weighted image demonstrates narrowing of the spinal canal at the craniocervical junction to 11 mm. Enlarged posterior longitudinal ligament. Myelopathy signal at the level of dens.

a massive prevertebral and minor epidural extension followed by the narrowed spinal canal with a sagittal diameter of 11 mm. Signs of myelopathy at the C1 level. The pathological change caused a shift in the anterior longitudinal ligament up to the C4 vertebra (Figures 2 a,b), PPD_3 showed normal reaction.

The inflammatory process was diagnosed and treated by cefotaxime 2.0 g/12 h, vancomycin 1.0 g/8 h and metronidazole 1.0 g/8h. The haemocultures were negative.

A surgical treatment was pursued urgently. The patient underwent the incision via an anterior, transverse approach to the upper cervical spine. After the incision of the abscess membrane, greyish pus was evacuated. The abscess was removed by carettage and aspiration. As the surgery was planned in two steps – decompression and then occipitocervical fixation – the instrumentation in the first step was not performed.

Postoperative complications were not registered and the clinical presentation improved. Pain in the neck decreased. The cervical spine was immobilized by a hard cervical collar. The antibiogram revealed *coagulase-negative Stahylococcus spp* as the cause of infection. The further therapy was continued with the same antibiotics. During the next ten postoperative days, the signs of tetraparesis were in gradual regression, while the laboratory indicators confirmed a decrease in infection.

During the night of the tenth postoperative day, however, the patient died. The autopsy performed revealed spinal cord tissue oedema, at the level of change, with overfilled blood vessels. In the upper spinal cord region, signs of myelopathy were evident, but not those of bleeding. There were no signs of pus penetration into the dural space (Figure 3a). Pyelonephritis was found, probably the cause of haematogenous spread of infection (Figure 3b).

Discussion

Coagulase-negative Stahylococcus, present in our case, is very rare as an agent of the spi-

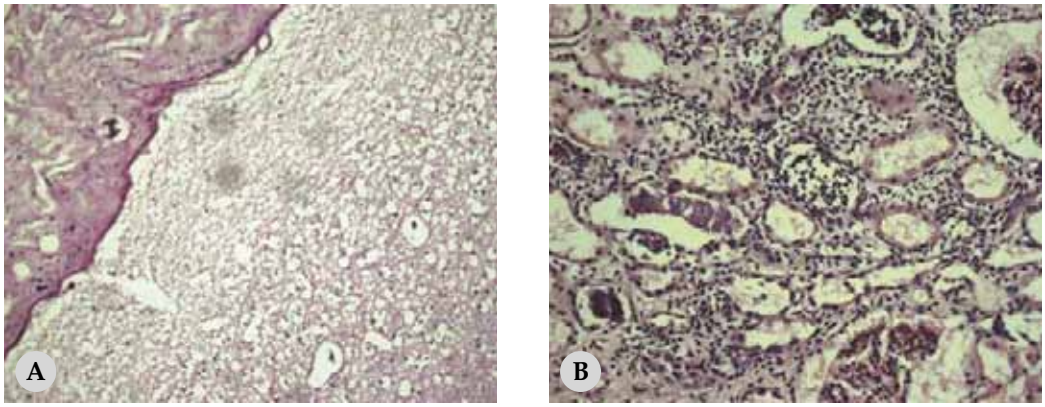

Figure 3. Microscopic images of the spinal cord and the kidney taken at autopsy:
A. Cross-sectional image of the spine cord at the craniocervical junction. Spinal cord edema. Presence of microthrombuses in some blood vessels obliterating the lumen. Pia mater is edematogenic with dilated blood vessels. Very close contact between the two maters around medulla, with partial obliteration of the subarachnoid space and pia and dura mater grown together.
B. Interstitial tissue of the kidney is edematogenic with dilated blood vessels and irregularly distributed granulocytic inflammatory infiltrator. Tubuli are characterized by serious parenchymatous degeneration of cells, while extended lumens are filled with homogenous eosynophilic cylinders. Glomeruli are intact.

nal infection. Hadjipavlou *et al.*[3] reviewed 34 cases of the spinal infection managed with the surgical percutaneous transpedicular drainage and found positive cultures in 73.5% cases out of which 16% case of infection with *coagulase-negative Stahylococcus* as the causative pathogen. A meta-analysis of 915 patients with the spinal epidural abscess, made by Reihsaus *et al.*[4] confirmed the pathogen in 753 cases, but only in 35 ones *coagulase-negative Stahylococcus spp* was found as an etiological factor.

The disease is usually insidious and progresses slowly over a long period of time so that in a large number of cases it has been recognized with a delay. Zigler *et al.*[5] described the difficulties a clinician is faced with in diagnosing this disease due to the atypical clinical presentation. Ross *et al.*[6] reported on a rarely present symptomatic triad for the early diagnosis of the disease - elevated temperature, neck pain, and progressive neurological deficit. Also, cervical spine lymphadenopathy, spasm of the neck musculature and progressive torticollis followed by subfebrility -as early symptoms of the upper cervical spine inflammation were described by Busche *et al*.[7]

Her diagnosis was "the neck pain syndrome", which was treated with the physical therapy for several months. The proper diagnosis of the disease was delayed for more than a year. Busche *et al*.[7] described a young man with diabetes and similar symptoms in the upper cervical spine of six months' duration before a sudden change for the worse and a proper diagnosis was made. Noguchi *et al*.[8] described the case of an elderly patient who complained of neck pain and stiffness of 7 days' duration and had symptoms of meningeal irritation. CT and MRI scans revealed odontoid osteomyelitis with the abscess. The authors recommend magnetic resonance imaging in the early stage of the disease emphasizing its important role in monitoring the disease evolution. Their diagnosis was based on CT and an early use of magnetic resonance imaging.[9,10]

Additional radiological diagnostics in our case was not adequately carried out. Plain X-ray of the cervical spine was taken

relatively early, a month after the onset of the symptoms, but was interpreted erroneously. On a lateral X-ray image, taken at that time, an increase in atlantodental interval for more than 2.5 mm can be seen, as a sign of anterior atlantodental subluxation. Neither an open mouth radiograph, which is standard in diagnostics of upper cervical spine pathology[10], nor dynamic lateral radiographs were taken. Abnormalities in the upper cervical spine region are frequently accompanied by abnormal parameters on plain radiographs even before clear clinical sympthomatology. In our case, the protrusion of the patient's head might have arisen additionally suspicion of the changes in the cervical spine. As shown in some biomechanical papers, alterations in the static alignment of the cervical spine segments as a result of the pathological process cause alterations in radiographic parameters on dynamic radiographs.

The patient did not receive immobilization for the following six months. The neurological symptoms got worse with the progression of the infection followed by destruction of ligaments and odontoid, due to the generated vertebral instability.[12] At the moment of her admittance, tetraparesis of spastic type was evident. Magnetic resonance imaging of the cervical spine revealed odontoid abscess and, therefore, the surgical therapy followed.

The untreated infection of the urinary tract, confirmed in our case by autopsy, probably triggered the occurrence of odontoid osteomyelitis. In 854 patients with the epidural spinal abscess, out of 377 extraspinal focuses of infection Reihsaus *et al*.[4] reported 23 urinary infections as the source of the abscess. The infection spread through the bloodstream contaminating the venous plexus of the occipitocervical region and further the epistropheus odontoid. Young and Weaver[13] stressed the patient's age (over 60 years), diabetes, oral infection, and medication misuse as crucial risk factors. Only the clinically undeveloped urinary infection as a cause of temporary bacteriuria was present. It was not, however, recognized as a possible focus of infection, and was left untreated, haemocultures were found to be positive in about two thirds of cases, but in our case they were negative.

The treatment of odontoid osteomyelitis with the abscess is controversial. Some authors emphasize successful clinical outcomes achieved in patients with vertebral osteomyelitis treated without surgery, especially in its early phase, when the segment is still stable.[14] However, successful outcomes by the operative treatment performed in one or two stages[5] have been reported in numerous recent papers. Neurological findings revealed a progressive cervical spine myelopathy, required an urgent surgical decompression in our patient. A two-step surgical treatment was planned, as suggested by Nakase *et al.*[15] We had no experience with anterior instrumentation at the C1/2 level. It seemed at that moment that a simultaneous posterior occipitocervical fixation would be too invasive for our patient. Therefore, the patient underwent the anterior decompression. Postoperatively, some signs of resolving of neurological deficits were registered, laboratory findings improved and the patient felt better.

Sudden death of the patient in spite of promising clinical course has not been described until now. Mortality caused by cervical spine osteomyelitis complicated by abscess accounts for 15% of all cases.[4] The autopsy revealed brain tissue swelling, ischemic necrosis at the site of spinal cord compression, and lung tissue swelling. No macroscopic changes in other organs were found, except for the right kidney pyelonephritis.

The abscess extended through the retropharyngeal space along the anterior longitudinal ligament up to the C4 level. The au-

topsy did not reveal the intradural abscess in the upper segment of the cervical spine cord. Probably sudden hypotension and respiratory arrest occurred during the spinal cord shock due to subarahnoidal inflammation of small blood vessels and their thrombosis.

Such a small blood vessels thrombosis may, or may not be seen macroscopically at autopsy. Brain swelling could also be a result of the intracranial complication of bacterial meningitis.[16] Neither clinical presentation of meningitis nor acute central cord syndrome was found in our patient. Probably the cause was the repeated compression of the spinal cord by unstable C1 segment. Such unstable segment, after decompression, caused repeated *microtraumas* - transient spinal cord ischemia, which led to blood vessel thrombosis in that part of the spine cord. Our case confirms that even in the situation of "partially repositionable" atlas subluxation there is a certain risk of the spinal cord compression, which can be fatal. This leads to a conclusion that the very evacuation of the granular tissue – as the first surgical act, can hide a potential risk of the additional destabilization of the segment and can impose a need for more secure postoperative stabilization of the cervical spine. The cervical spine orthosis, provided here, proved as unsatisfactory. Postoperatively, it was necessary to use, up to the following surgical step, halo-traction or halo traction-apparatus. Additionally, diagnostic and therapeutic overlooks, which to a great extent contributed to such an outcome, remind us of the fact that the patient should always be considered as a whole, and especially in cases of the treatment of so severe infections.

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research article

Imaging in nasopharyngeal carcinoma: the value of 18-Florine Fluorodeoxyglucose PET/CT in comparison to conventional imaging modalities CT and MRI

Abdul Jalil Nordin[1], Simona Secondino[2], Noraini Abdul Rahim[3], Paolo Pedrazzoli[2], Salvatore Siena[2], Claudio Rossetti[4], Tahir Aris[5]

[1]Nuclear Imaging Unit, Faculty Medicine and Health Science, University Putra Malaysia [2]Oncologia Medica Falck, Ospedale Niguarda Ca' Granda, Milan, Italy [3]Radiology Department, Hospital Serdang, Serdang, Malaysia [4]Department of Nuclear Medicine, Ospedale Niguardia Ca' Granda, Milan, Italy [5]Institute for Health Systems Research, Ministry Of Health Malaysia

Background. *The aim of the study was to evaluate the clinical usefulness of 18F Fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET/CT) in the management of nasopharyngeal carcinoma (NPC) in comparison to conventional imaging modalities.*

Methods. *This retrospective study was done at Ospedale Niguarda, Milan, Italy. Data were acquired from 24 NPC patients between May 2003 and December 2006. They had FDG PET/CT and CT or MRI during the initial diagnosis and at follow-up. Each finding was tabulated and compared with tissue biopsy at diagnosis and clinical status during the follow up after the therapy. A statistical calculation was done to derive the value of each modality.*

Results. *The sensitivity and accuracy of PET/CT and CT/MRI were equally high at diagnosis. At the follow up, a negative PET/CT finding suggested a complete remission with sensitivity and negative predictive value of 100%.*

Conclusions. *18F FDG PET/CT is a potential modality to be utilized in following up NPC patients for evaluating a response to therapy.*

Key words: positron emission tomography; computed tomography; magnetic resonance imaging; nasopharyngeal carcinoma; follow-up

Introduction

Nasopharyngeal carcinoma (NPC) is common among the Chinese populations especially in the south China and South East Asia region with incidence of 20 to 50 per 100 000 individuals.[1,2] Despite being uncommon among other ethnic groups including the Europeans, a higher incidence

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Correspondence to: Abdul Jalil Nordin, MD, Nuclear Imaging Unit, Faculty Medicine and Health Science, University Putra Malaysia, 43400 Serdang, Selangor, Malaysia; E-mail: drimaging@yahoo.com

has been reported among the south Indian community as well as in the North African community.[3]

Ebstein Barr Viral (EBV) infection is thought to play an important role in initiating the development of this tumour. Multiple literature review revealed the coexistence between EBV infection and NPC.[4-10] There is a huge clinical value of the data about EBV infection, because no factor in a wide spectrum of biochemical and histological candidate-markers has yet been identified to predict reliably the natural course of the disease or its response to the therapy to be used in the routine clinical practice,[11] but, Kenneth *et al.* suggested that EBV status could be a reliable predictor for the overall survival of NPC patients.[12]

Most NPC patients commonly manifest themselves with painless enlarged lymph nodes in the neck which are often bilateral. When these are in association with positive EBV's DNA, they are highly suspicious for nodal disease from NPC primary.[13] Other clinical features include nasal obstruction and epistaxis which may occur as a result of the local tumour infiltration. Patients may also suffer from hearing problems like hearing loss, tinnitus or recurrent *otitis media*. In advanced cases, the cranial nerve dysfunction may occur. A more generalized presentation like sore throat and headache are not uncommon. These clinical presentations are looked for at diagnosis and follow up.

Besides histological typing, the early detection and accurate staging at diagnosis and restaging at follow up are important prognostic determinants. Early and accurate staging at diagnosis will ensure proper treatment deliveries as the prevalence of head and neck metastases is as high as 40% at the time of the initial presentation. Accurate restaging after therapy is also important to determine the treatment response and to answer the question whether the patient requires a change in the pre planned treatment regime.

In the current practice, conventional imaging modalities like CT and MR are routinely employed to assist clinicians in staging NPC patients. A fused integrated morphological and functional imaging modality of positron emission tomography / computed tomography (PET/CT) is another possible useful new tool to be utilized in the assessment of NPC patients like in other oncological patients.[14] This study was conducted in view to evaluate the role of fused PET/CT in the management of NPC patients.

This study was approved by the institutional review board of the hospital.

Patients and methods

Patients

Retrospective data from 33 patients between May 2003 to December 2006, from Nuclear Medicine Department, Ospedale Niguarda, Milan, Italy were reviewed. These are confirmed cases of nasopharyngeal carcinoma from histopathological tissue biopsy. The results were collected and tabulated.

Since this study was selective for comparison between PET/CT and conventional imaging tools, only paired PET/CT with CT or MRI imaging results were included. Patients with incomplete imaging data were excluded from this study. Finally, we selected imaging results from 24 patients for the analysis. There were 7 women and 17 men, age between 21-75 years included in the study. Patients were grouped into three categories.

Group A patients had a combination of examinations consisting of 18F-FDG PET/CT, CT and or MRI examinations at diagnosis and after the treatment. These patients received radio or chemotherapy singly or in combination following the confirmation of the diagnosis of NPC. Post therapy imag-

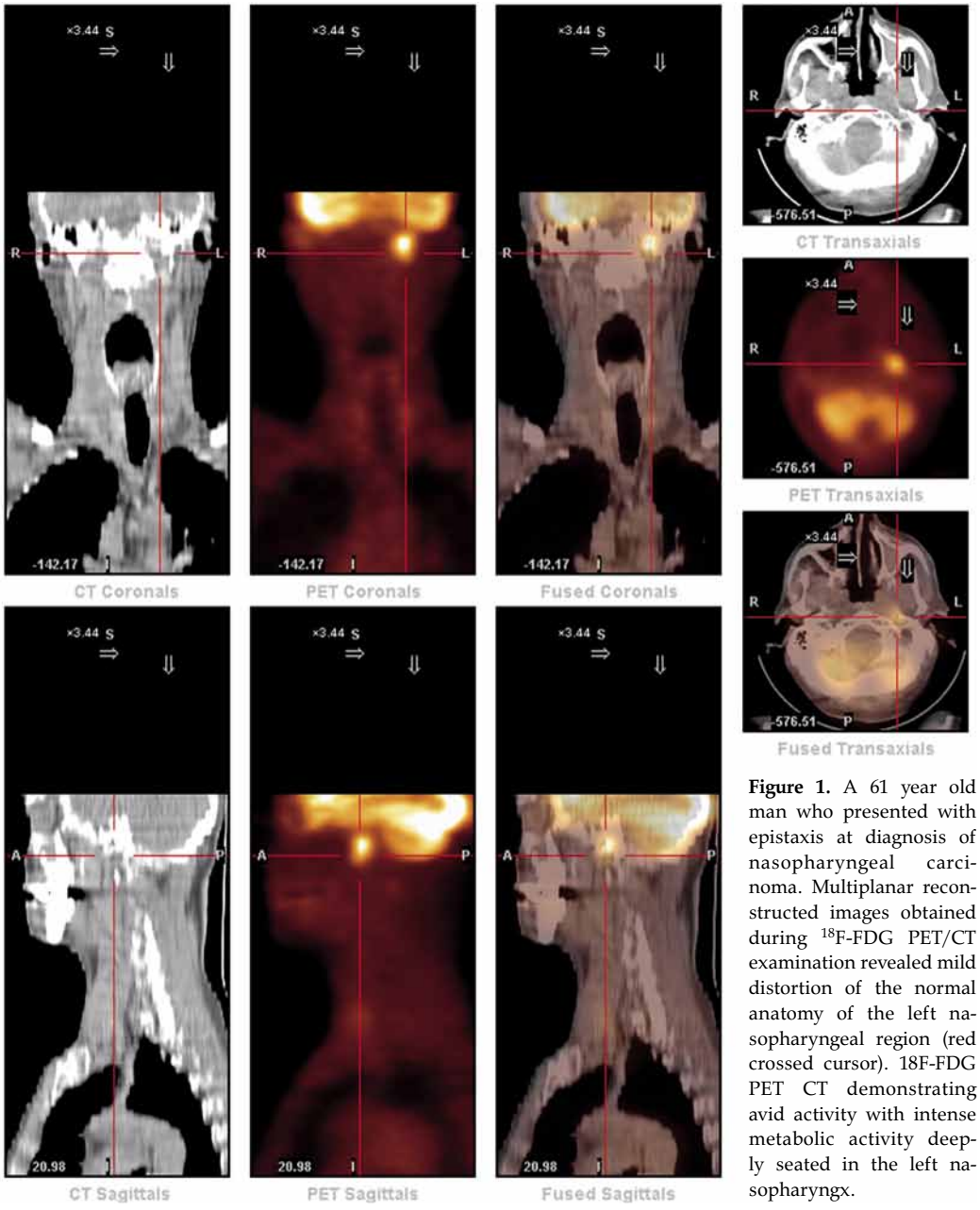

Figure 1. A 61 year old man who presented with epistaxis at diagnosis of nasopharyngeal carcinoma. Multiplanar reconstructed images obtained during ^{18}F-FDG PET/CT examination revealed mild distortion of the normal anatomy of the left nasopharyngeal region (red crossed cursor). 18F-FDG PET CT demonstrating avid activity with intense metabolic activity deeply seated in the left nasopharyngx.

ing was conducted at 5 - 6 months upon the completion of the last treatment.

Group B patients consisting only newly diagnosed NPC patients and had a combination of examinations at the initial staging process. These patients are still under follow up. They will be reassessed during their next follow up visit to the clinic. Thus, there is only one PET/CT study performed at diagnosis.

Table 1. Clinical, histopathological and imaging results

		At diagnosis			Following treatment		
Group A	**Age/Sex**	**PET/CT**	**CT/MR**	**HPE**	**PET/CT**	**CT/MR**	**Disease status**
1	64/M	pos	pos	und	neg	neg	remission
2	63/M	pos	pos	und	pos	pos	persistent
3	61/M	pos	pos	few diff	pos	pos	persistent
4	53/M	pos	pos	N/A	pos	pos	persistent
5	48/M	pos	pos	few diff	pos	pos	persistent
6	39/F	pos	pos	und	pos	pos	remission
7	51/M	pos	pos	und	pos	pos	persistent
8	62/M	pos	pos	und	pos	pos	persistent
9	75/M	pos	pos	few diff	pos	pos	persistent
10	47/F	pos	pos	und	neg	neg	remission
11	37/F	pos	pos	und	pos	pos	persistent
12	63/F	pos	pos	und	pos	neg	persistent
13	21/F	pos	pos	und	pos	pos	persistent
Group B							
14	61/F	pos	pos	und	n/a	n/a	n/a
15	64/M	pos	pos	und	n/a	n/a	n/a
16	52/M	pos	pos	und	n/a	n/a	n/a
17	45/M	pos	pos	und	n/a	n/a	n/a
18	63/M	pos	pos	und	n/a	n/a	n/a
Group C							
19	54/M	n/a	n/a	und	neg	neg	remission
20	45/M	n/a	n/a	und	pos	pos	persistent
21	46/M	n/a	n/a	und	neg	neg	remission
22	44/F	n/a	n/a	und	pos	pos	persistent
23	60/M	n/a	n/a	und	pos	neg	persistent
24	60/M	n/a	n/a	und	neg	neg	remission

F=female, M=male, pos=positive, neg=negative, und=undifferentiated, diff=differentiated, n/a=not available

Group C patients had their combined examinations done during the post therapy. PET/CT was not performed at the earlier stage before the treatment as the facility was not accessible.

At presentation, the diagnosis of each patient was confirmed through the histopathological examination of tissue biopsy at Ospedale Niguarda in Milan or elsewhere and referred to the centre for the further evaluation and follow up.

Upon completion of the full course of radiotherapy or combined chemotherapy, group A and Group C patients were reassessed by the clinicians during the follow up visit at the clinic when they returned for the clinical assessment. Clinical signs and symptoms of recurrence like pain, epistaxis, neurological deficit or evidence of hearing impairment were sought for. The endoscopic examination looking for a direct evidence of the recurrent disease performed prior to

imaging studies. In the routine practice, during the follow up, close monitoring for tumour recurrence or progression were accomplished using CT or MRI. In doubtful imaging findings, other than undergoing PET/CT examination, patients underwent biopsy. Eventually, the final diagnosis of the patient was made based upon the clinical evaluation as stated in the 'Disease status' column in Table 1.

18F-FDG PET/CT imaging

Whole body FDG PET/CT scan was done at The Department of Nuclear Medicine, Ospedale Niguarda , Milan, Italy using integrated PET/CT system (Biograph, Siemens) combine dual slice spiral CT with a dedicated full-ring Bismuth Germanate (BGO) crystal for the PET scanner.

Following overnight fasting, PET/CT image acquisition was accomplished after 60 minutes waiting time following intravenous FDG injection. All examinations performed without intravenous contrast administration using the following protocol:

- CT Scanogram performed for planning the CT and PET study.
- A low dose CT acquisition was done first with parameters of 2.5 mm slices, spiral mode at 50 mAs and 130 kV for the anatomical correlation and attenuation correction of PET images. Immediately after CT acquisition, the table was positioned for PET acquisition. PET image acquisition was done at 5 min per bed position.
- A first acquisition was performed from the lung to the thighs in 3-dimensional mode. The second acquisition was performed from the vertex of the skull to the thoracic inlet.
- The reconstruction of the emission data was performed by using an iterative algorithm with software Somaris/5 VA40C and stored in a 128 matrix. CT-data were used for the attenuation correction. Volume projected images (transaxial, coronal and sagittal slices) and fusion images were generated for the interpretation.
- In post therapy patients, PET/CT imaging was done 20-24weeks post treatment, to avoid false positive results.

Image interpretation and data analysis

In our study, we include 37 paired imaging examinations. These consist of PET/CT with CT or with MRI. Each method was interpreted separately and independently to assess primary tumour and cervical node status at two different stages, at the initial diagnosis and the following therapy by three experienced PET/CT specialists. Observation also includes evidence for distant metastasis.

On PET/CT images, results were derived from the visual analysis. Areas of the increased uptake, other than the normal physiological distribution, were considered as pathological. This was further confirmed through the semi quantitative analysis on the region of interest using Standardized Uptake Value (SUV). A value of more than 2.5 was pathological.

On CT or MR images, any pathological alterations to the normal anatomical boundaries as evident by distorted outline or presence of enhancing lesions in the studied areas are considered as pathological. Observations also include abnormal neck lymphadenopathies exceeding 10 mm in diameter. Lymph nodes of any size with central necrosis are also regarded as pathological.

Statistical Analysis

All the findings were tabulated to calculate the sensitivity, specificity and accuracy of the imaging modules. The negative and positive predictive values derived from these data.

Results

Patients

From selected 24 patients in our study, we included 37 paired examinations of PET/CT and CT or MRI. At diagnosis, the imaging results were compared with histopathological findings. At follow up, the standard was taken as the final clinical conclusion of disease status done by the clinicians following the clinical assessment. The summary of the findings of all enrolled patients are summarized in Table 1.

There were 17 (65%) males and 7 (35%) female patients. The age distribution was between 21 to 70 year-old with the highest frequency of patients aged at 61 years and above (Table 2).

Table 2. Age distribution

Age (years)	Frequency	Percentage
<30	1	4
31-40	2	8.5
41-50	6	25
51-60	6	25
61 and above	9	37.5
Total	24	100

Comparing results between imaging modalities at diagnosis

All 18 results at diagnosis were found to be concordant between PET/CT and CT or MRI. When these results were compared with standard (tissue biopsy), the calculated sensitivity and accuracy were found to be equally high (Table 4). Since there were no false negative or false positive results, the specificity is statistically void.

Comparing results between imaging modalities for the assessment of the treatment response

At imaging after the therapy, both methods are found to be equally accurate with high positive predictive values. The negative predictive value for PET/CT is found to be higher than the conventional imaging modalities (100.0% for PET and 71.0% for conventional imaging) (Table 4). Overall, PET/CT provides a higher sensitivity in detecting the local recurrence disease as compared to the conventional imaging modality.

Discussion

Accuracy in staging NPC is most crucial during the post therapy evaluation at the follow up study. Centrally necrotic cervical nodes following the therapy may resemble the disease progression. The situation can be further complicated with the presence of reconstructive surgical procedures using graft and flap in this region.

While conducting this study, we found more significant variations in imaging results during the post treatment evaluation with a good statistical consensus at diagnosis.

There are no significant indifferences in the results at diagnosis since our study comprised of small number of patients. Furthermore, this retrospective selection of cases did not reflect the actual progress of clinical work flow for the patients investigated for suspicious NPC. This includes the identification of infected neck nodes or other nearby pathology at imaging which may resemble the clinical presentation of NPC. These are major contributions towards the variation in the statistic analysis.

In the post therapy evaluation of both imaging modalities at follow up, we found two false negative results on conventional imaging modalities (patient 12 and 23) and 1 false positive result on both imaging modalities including PET/CT (patient 6).

We re-evaluated the retrospective false negative results of the two patients on conventional imaging modalities and reach to

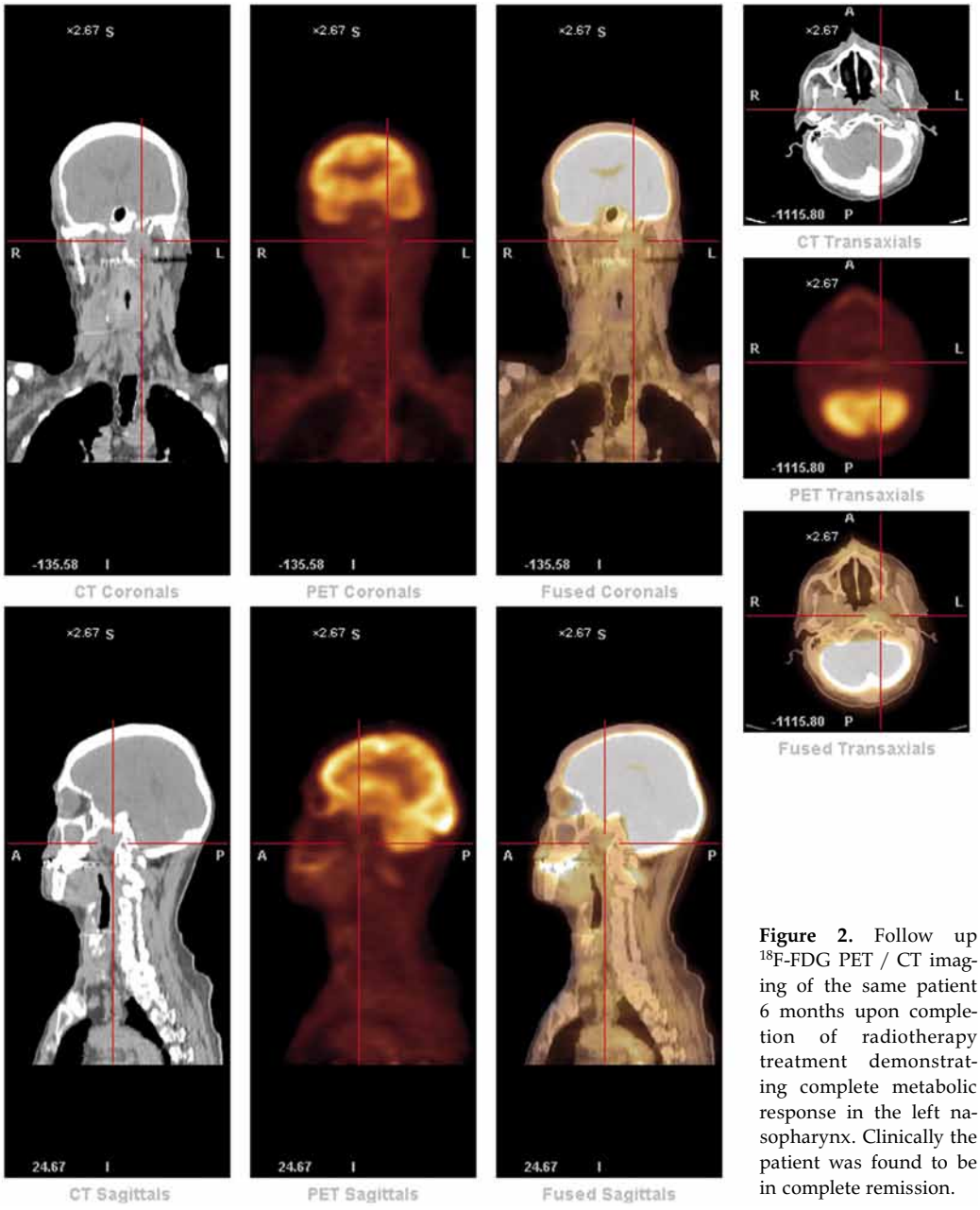

Figure 2. Follow up ^{18}F-FDG PET / CT imaging of the same patient 6 months upon completion of radiotherapy treatment demonstrating complete metabolic response in the left nasopharynx. Clinically the patient was found to be in complete remission.

an agreement that there were no significant anatomical disruption noted in the nasopharyngeal areas. Furthermore, no loco regional nodal involvement demonstrated in these patients. Thorough the search by the direct endoscopic visualization were the imaging findings confirmed. However, PET/CT evaluation demonstrated the lesion with a high metabolic activity indicating recurrent NPC. This particular clinical ex-

Table 3. Comparative evaluation results between imaging modalities at diagnosis

Modality	TP	TN	FP	FN	Sensitivity %	Specificity %	Accuracy %
CT/MR	18	0	0	0	100	null	100
PET/CT	18	0	0	0	100	null	100

TP=true positive, TN=true negative, FP=false positive, FN=false negative

Table 4. Evaluation results for treatment response assessment between imaging modalities

Modality	TP	TN	FP	FN	Total exam	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %
CT/MR	11	5	1	2	19	84	83	84	92	71
PET/CT	13	5	1	0	19	100	83	84	93	100

TP=true positive, TN=true negative, FP=false positive, FN=false negative, PPV=positive predictive value, NPV=negative predictive value

ample has been described previously where 15.4% prevalence of residual or recurrent tumours are found to be beyond the reach of the routine nasopharyngeal biopsy.[15] Therefore, the clinical assessment via endoscopic examination may missed deeply seated tumours whilst early tumour development may not manifest themselves clinically. Since conventional imaging modalities like CT or MRI are much dependent on anatomical alterations to be readily identified at imaging, this clinical example may have resulted in understaging or missed tumour lesions.

We also performed the re-evaluation study on the imaging results of the other patient. Because of doubtful positive imaging findings in the absence of signs and symptoms of the disease recurrence, the patient underwent biopsy of the nasopharynx which result was later found to be negative. The remission state was later confirmed at the subsequent follow-up. Thus, our reviewers came to an agreement that the altered anatomical landmark with reactivity following radio- and radio/chemotherapy may have been the cause for the false positive interpretation. Although we follow standard recommendations to perform imaging studies after 6 to 8 weeks post therapy period, variations in the rate of recovery and body response towards injury events caused by radiation or chemotherapy may differ from one patient to another.[16,17] In addition, the possibility of a brief episode of the local inflammatory reaction at the time of imaging as a result of the infection cannot be totally segregated from the fact that there is a high metabolic activity in PET image acquisition.

The literature search suggested 18F-FDG PET was more specific than conventional imaging modalities in detecting residual or recurrent nodal metastasis in head and neck malignancies. The sensitivities in these articles cited ranging from 67% to 100% and specificities ranging from 77% to 100%.[18-22] Our results are comparable with these findings (sensitivity 100% and specificity 83%) supporting the assertion that 18F-FDG PET should be a sensitive tool in detecting residual or recurrent nodes in NPC. In fact, by incorporating CT into functional PET imaging, the percentage is expected to be higher as compared to PET imaging alone. The ability of PET in providing the functional metabolic activity of tumour infiltrated structures including small nodes is being utilized to enhance the superior capability of CT in demonstrating the precise anatomical location of these lesions. Thus, they

are readily detectable on PET imaging and independent on the morphological changes in CT or MR images. The fusion of both imaging modalities in an integrated PET/CT machine should give better results.[14,23-25] Furthermore, useful information can be obtained during a single seating and also time saving for the patient's convenience.

Within our small study population, we also demonstrated a higher negative predictive value of PET/CT in comparison to conventional imaging methods (Table 4). This finding signifies a more reliable negative PET/CT imaging result in circumstances when the actual disease is absent where the conventional imaging modality may have 29% chances of the false negative interpretation.

Our study encourages the use of PET/CT in the post therapy management of NPC patients. We demonstrated the ability of PET/CT in correcting tumour under staging in two of our patients whose results were found to be falsely negative using the conventional imaging modality (patient 12 and 23). Aside from the treatment response assessment, PET/CT findings can also lead the clinicians in decision making on the choices of the clinical approach to be adopted. In the absence of clinical findings, a positive PET/CT result can be used as a general indicator for a more aggressive approach like biopsy in order to confirm the final diagnosis (patient number 6). This modality should be recommended as a preferable tool at follow up.[26,27]

Even though our findings at the post therapy assessment are relatively relevant, we suggest more research being granted for the assessment of actual value of PET/CT in therapy response within a larger cohort group of NPC patients.

Conclusions

The study found 18F-FDG PET/CT a suitable imaging modality to be utilized in managing patients with NPC especially at the post therapy follow-up. Further evidence is required to seek the actual value of this imaging modality at the initial stage of diagnosis and follow up within a larger cohort group.

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research article

Negative predictive value of F-18-FDG coincidence PET in patients with Hodgkin's disease and a residual mass after therapy: a retrospective diagnostic test study

Dražen Huić[1], Andrea Mutvar[1], Sandra Kinda-Bašić[2], Igor Aurer[2], Martina Ciglar[1], Darko Grošev[1], Ivo Radman[2], Boris Labar[2], Damir Dodig[1]

[1]Department of Nuclear Medicine and Radiation Protection, [2]Department of Internal Medicine, Division of Hematology, Zagreb University Hospital Centre, Zagreb, Croatia

Background. *The aim of the study was to asses the negative predictive value (NPV) of FDG-PET performed with triple-head coincidence gamma camera after the first-line therapy or salvage therapy in patients with Hodgkin's disease (HD) compared by a long-term follow-up as a reference standard.*

Methods. *This retrospective diagnostic test study was done at the University Hospital Centre Zagreb between June 2001 and February 2008. The charts of 131 consecutive patients with Hodgkin's disease were reviewed. Seventy-three consecutive PET-negative patients (median age 28 years; range 12-80 years) with primary or recurrent biopsy confirmed lymphoma after the first-line therapy or salvage therapy were followed-up at least 12 months (median 23 months; range 12-69 months). All already performed ^{18}F-FDG PET scans (using hybrid PET camera with triple head coincidence imaging capability within a few months after the completion of the therapy) were again visually interpreted by two board-certified nuclear medicine physicians who were blinded to any clinical or CT data. The negative predictive value of FDG-PET performed with triple-head coincidence gamma camera (Index test) was compared with a long-term follow-up as a reference standard.*

Results. *Out of 131 patients 73 turned-out to be PET-negative. Of those 73 PET-negative patients, 61 have been scanned after the first-line chemotherapy/radiotherapy, and only 3 of them relapsed in a follow-up (negative predictive value 0.95). Twelve patients with resistant disease have been scanned after the repeated therapy, and 4 of them relapsed in a follow-up period (negative predictive value 0.66).*

Conclusions. *This methodology with a triple-head coincidence gamma camera has a high negative predictive value. A negative PET scan can reassure patients and their doctors that the disease is not active.*

Key words: Hodgkin's disease; fluorine-18-fluorodeoxyglucose; FDG; PET; therapy monitoring; prognosis; follow-up; negative predictive value

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Correspondence to: Dražen Huić, MD, PhD, Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Centre, Kišpatićeva 12, 10000 Zagreb, Croatia; Phone: +385 1 23 88 086; Fax: +385 1 24 21 874; E mail: dhuic@kbc-zagreb.hr

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Introduction

Hodgkin's disease (HD) is a highly curable malignancy. With the modern therapy a disease-free survival is around 80% at 5 years.[1] However, HD survivors face significant medical problems related to toxicities of chemo- and radiotherapy, including secondary primary malignancies, cardiovascular and endocrine problems.[2] Therefore, avoiding an unnecessary therapy is very important.[3]

Accurate staging is essential for optimizing the patient's therapy but the main dilemma in assessing response at the end of the treatment is the presence of residual mass. In the large percentage of patients (> 60%) conventional imaging methods show remaining tumour masses at the end of the therapy, although only a small percentage of these patients still have the active disease and eventually will relapse.[1,4,5]

Computed tomography (CT) has long been the standard procedure for staging, therapy monitoring and follow-up of lymphoma patients, but it has well-known limitations, caused by the fact that the differentiation between normal and abnormal findings is based exclusively on lymph node size, and cannot differentiate scar tissue from viable tumour in the residual mass.[3,6,7]

Metabolic imaging using fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET provides a functional characterization of tissue and assesses tumour viability unrelated to morphologic criteria.[8,9] High accuracy of FDG-PET in characterization of residual masses and early detection of recurrent disease cause this imaging method to have an important role in the management of lymphoma by enabling a more precise and accurate determination of the disease status. The accurate assessment of response at the end of the therapy is of considerable prognostic importance because it can enable physicians to withhold the unnecessary additional radiotherapy or even high-dose chemotherapy and autografting and, thus, spare the patient's acute and late toxicity.

Numerous studies and two recent meta-analyses confirm a high negative predictive value (NPV) of FDG-PET performed using dedicated PET scanners in patients with HD.[4,10-12] The same is not true for positive FDG-PET findings and generally, in such cases a biopsy is recommended for the confirmation of presence of the active disease.[11-14]

It is well known that coincidence gamma cameras have inferior sensitivity for the tumour detection in comparison to dedicated PET scanners.[15,16] Therefore, some authors expressed doubts about the value of coincidence FDG-PET scanning for the response assessment in patients with lymphoma.[17,18]

The aim of this study was to asses the negative predictive value (NPV) of FDG-PET performed with a triple-head coincidence gamma camera after the first-line therapy or salvage therapy in patients with HD compared by a long-term follow-up as a reference standard.

Patients and methods

Design and setting

This retrospective diagnostic test study was done at the University Hospital Centre Zagreb between June 2001 and February 2008.

Patients

One-hundred thirty-one patients with a residual mass after the treatment of HD from our or collaborating centres had a FDG-PET scan performed at our centre. All patients had pre-therapy biopsy – proven HD. Initial staging consisted of a careful

clinical examination of peripheral lymph node areas, CT scanning of the thorax, abdomen and pelvis and a bone marrow biopsy. Those examinations that were positive prior to the treatment were repeated during restaging. Patients with a lymph node visible on a CT-scan bigger than 1.5 cm in the greatest diameter were considered to have a residual mass.[19]

Only the follow-up of 73 PET-negative patients was analyzed. In 61 patients the initial PET study was performed after the front-line therapy and in 12 after the salvage therapy. The follow-up of patients was at least 12 months (median 23 months; range 12-69 months).

FDG-PET

All PET studies were performed using IRIX hybrid PET camera (Philips Medical System, USA) with triple head coincidence imaging capability and equipped with parallel slat collimators. Its improved electronics for the coincidence detection allows the detectors to reject any events that normally would have caused pile-up and mispositioning. A detailed system description and performance characteristics are given elsewhere.[20,21]

About 370 MBq (10 mCi) of ^{18}F-FDG was administered intravenously to each patient after overnight fasting. Patients received a diuretic to minimize artefacts due to urinary stasis and were kept well hydrated. Between injection and scanning patients lied still to avoid FDG muscular uptake. Sixty minutes post injection two tomographic acquisitions of the neck, thorax, abdomen and groins were done, 30 min duration each, using angular step 3^0, with all three camera heads making full 360^0 rotation in rectangular configuration (heads 2&3 parallel to each other, head 1 perpendicular to heads 2&3). After the acquisition, raw list mode data were rebinned into SPECT-like projections (matrix: 128x128, zoom=1.0) using single slice rebinning algorithm (axial acceptance angle 12^0). The images were iteratively reconstructed. No attenuation correction was used.

Interpretation of ^{18}F-FDG PET scans

All already performed ^{18}F-FDG PET scans were visually interpreted again by two board-certified nuclear medicine physicians (D.H., with 9 years of FDG-PET experience; A.M. with 5 years FGD-PET experience) who were blinded to any clinical or CT data. A positive result was defined as the focal activity higher than that of surrounding background tissue not located in areas of physiological ^{18}F-FDG uptake, without similar activity seen on the contra lateral side. A negative result was defined as no abnormal ^{18}F-FDG uptake at any side.

Ethics

A signed informed consent for imaging and using the patient's data for the further research was obtained from all patients. The study was approved by the Ethics Committee of University Hospital Centre, Zagreb.

Statistical analyses

The values are expressed as negative predictive values (NPV) with 95% confidence intervals (CI) by using the exact binomial method.

Results

Out of total 131 patients 58 patients turned-out to be PET-positive, and were not included in the study. The demographic and clinical data of 73 PET-negative patients are presented in Table 1. Their median age was 28 years (range, 12-80 years). At diag-

nosis 3 patients were in stage I, 46 in stage II, 16 in stage III and 8 in stage IV. ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) was the most frequently used front-line treatment. Patients in stage I and II generally received 4 cycles of ABVD and involved-field irradiation and those in stage III and IV 6 to 8 cycles of ABVD. Patients who had a negative PET scan received no further antitumor therapy until relapse.

Flow diagram of our patients is presented in Figure 1. Seven patients (out of 73) relapsed (NPV = 0.90; CI: 0.81-0.96), three (out of 61 patients) after the front-line treatment (NPV = 0.95; CI: 0.86-0.99) and four patients (out of 12) after the salvage therapy (NPV = 0.67; CI: 0.35-0.90).

Table 1. Demographic and clinical characteristics of PET-negative patients with Hodgkin's disease (N=73)

Characteristics	Values
Median age (years)	28 (range 12-80)
Sex	
Male	36
Female	37
Histology	
Nodular sclerosis	52
Mixed cellularity	10
Lymphocyte rich	1
Not available	10
Ann Arbor clinical stage	
I	3
II	46
III	16
IV	8
B symptoms	
Yes	38
No	35
Treatment	
Chemotherapy alone	24
Chemotherapy and radiotherapy	49
Follow-up after PET (months)	
Median	23
Range	12-69

Discussion

The results show that FDG-PET performed in HD patients with a residual post treatment tumour mass using a triple-head coincidence gamma camera has a high NPV (0.90). This is especially true for front-line patients where it reaches 0.95. Thus, our results in these patients are comparable to results obtained with dedicated PET systems with NPVs between 0.90 and 0.96.[4,7,10,22] Lower NPV (0.66) in patients receiving salvage therapy can be expected because of a more aggressive disease course.

We have decided not to analyze the PET positive patients in detail because, after scanning, they were not treated in a uniform way. Thus, it would be very hard to discern the true positive predictive value of a positive PET scan. Furthermore, we are missing gold standard (biopsy) for the really active disease. Besides, because of physiological variants, false-positive FDG uptake is predominantly due to post-therapy inflammatory changes, which subsequently resolve.[23,24] The body of evidence about false positive post treatment PET in patients with HD is constantly growing,[12-14,18] and to gain accurate data FDG-avid lesions must be checked by biopsy, specially in previously unaffected region.[3,4,10,12-14,18,23,25] Noninvasive alternative is to wait and repeat PET imaging in one or two months.[24]

This study has several limitations including a retrospective design, relatively small sample size reflecting the low incidence of HD and aggregation of patients with varying disease stages and treatment regimens. The PET equipment used was outdated lacking attenuation correction. Still, the high NPV indicates that coincidental PET scanning might be as reliable as dedicated PET or PET/CT systems, at least in patients with HD with a residual mass after the ini-

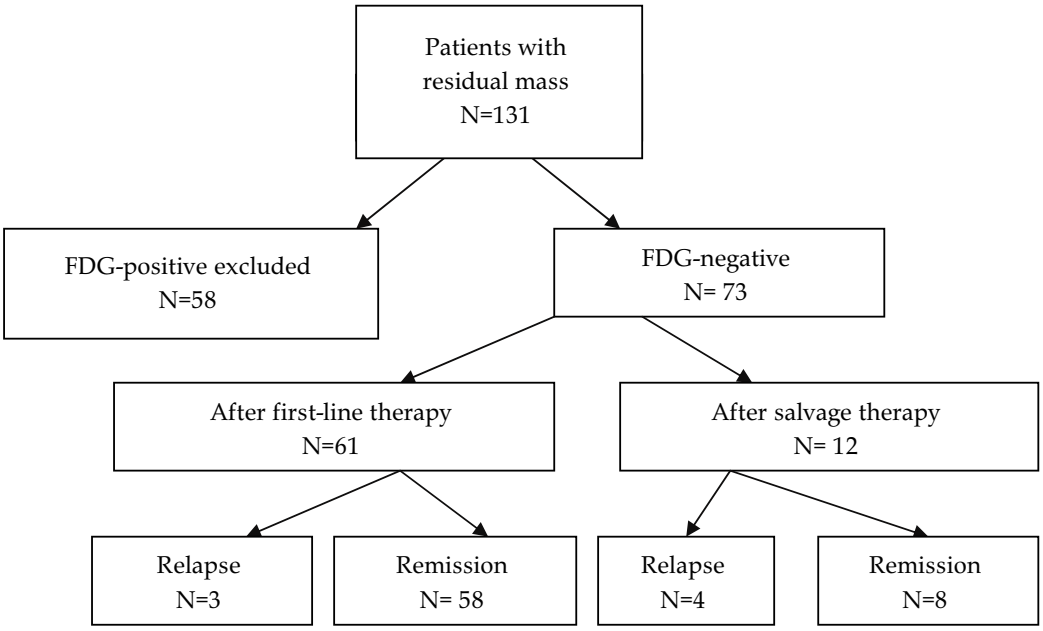

Figure 1. The flow diagram of primary or recurrent Hodgkin's disease (HD) patients with residual mass and FDG-PET scan after first-line or salvage therapy.

tial therapy. This means that coincidence PET can be a viable alternative for those centres which do not have an easy access to dedicated PET or PET/CT systems, which is wildly used.[8] In this constellation is a negative PET scan an important contribution in the management of patients and can provide reassurance to both, patients and their doctors, that disease is not active.

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research article

Enhanced cytotoxicity of bleomycin and cisplatin after electroporation in murine colorectal carcinoma cells

Vesna Todorovic[1], Gregor Sersa[1], Karel Flisar[3], Maja Cemazar[1,2]

[1] University of Primorska, College of Health Care Izola, Izola, [2] Institute of Oncology Ljubljana, Ljubljana, [3] University of Ljubljana, Faculty of Electrical Engineering, Ljubljana, Slovenia

Background. *Electrochemotherapy is a local treatment combining application of electric pulses and chemotherapy. Two chemotherapeutic drugs, bleomycin and cisplatin, have proved to be effective in electrochemotherapy. The effectiveness of electrochemotherapy was demonstrated in the treatment of various cutaneous and subcutaneous tumours in cancer patients. Only a few preclinical studies were performed in colorectal carcinoma, mostly using bleomycin. Our aim was to evaluate the sensitivity of the murine colorectal carcinoma cell line CMT-93 to electrochemotherapy with bleomycin and cisplatin for potential use in preclinical and clinical studies.*

Methods. *CMT-93 cells were exposed to either the chemotherapeutic drug alone or electrochemotherapy. A clonogenic assay was used to determine cell survival after treatment. Apoptosis was measured by caspase-3/7 activity, necrosis by changes in cell morphology and cell viability by the MTS assay 16 hours after electrochemotherapy.*

Results. *Cells treated with electrochemotherapy were 500-fold more sensitive to bleomycin and 2.8-fold more sensitive to cisplatin compared to cells treated with the drugs alone. At the highest concentrations, a significant reduction in cell viability, increase in caspase-3/7 activity and necrotic cells were observed after electrochemotherapy.*

Conclusions. *Exposure of cells to electric pulses enhanced cytotoxicity of both bleomycin and cisplatin. Reduced cell viability was due to apoptotic and necrotic cell death. Furthermore, electrochemotherapy with bleomycin was more cytotoxic than electrochemotherapy with cisplatin in this colorectal carcinoma cell line.*

Key words. *electroporation; electrochemotherapy; colorectal carcinoma; bleomycin; cisplatin*

Introduction

Electroporation is the application of electric pulses to cells *in vitro* or tumours *in vivo*. It is effective in facilitating the transport of different molecules with otherwise hampered transport across the plasma

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Correspondence to: Prof. Maja Cemazar, PhD, Institute of Oncology Ljubljana, Zaloska cesta 2, SI-1000 Ljubljana, Slovenia. Phone +386 1 587 95 44; E-mail: mcemazar@onko-i.si

membrane, including chemotherapeutic drugs.[1,2] Electroporation can be used in combination with chemotherapy (electrochemotherapy) or gene therapy (electrogene therapy) to increase the uptake of chemotherapeutic drugs, or nucleic acids, respectively. So far, two chemotherapeutic drugs have proved to be effective in electrochemotherapy, bleomycin (BLM) and cisplatin (CDDP). Electroporation with BLM or CDDP significantly enhances the cytotoxicity of these drugs in different tumour cell lines, also of CDDP-resistant cell lines and solid experimental tumours.[3-6] Furthermore, its effectiveness was demonstrated in the treatment of various cutaneous and subcutaneous tumours of various malignancies.[7,8]

Colorectal carcinoma is one of the most common cancers worldwide, and its incidence is increasing. Traditional treatment modalities for colorectal carcinoma are surgery, chemotherapy and/or radiation. However, not all patients can undergo surgery due to severe complications, such as chronic heart failure, chronic renal failure, and chronic obstructive pulmonary diseases.[9] Chemotherapy can be used for these patients, yet its effectiveness is limited by side effects. However, if further progress in reducing colorectal carcinoma mortality is to be accomplished, new treatment strategies are needed.

Electrochemotherapy could provide an innovative therapeutic approach for the treatment of colorectal carcinoma. The majority of studies evaluating the antitumour effect of electrochemotherapy concentrated on cutaneous and subcutaneous tumours of various histology, and only a few on colorectal carcinoma.[9,10] Therefore, the aim of our study was to evaluate the *in vitro* sensitivity of the murine colorectal carcinoma cell line CMT-93 to electrochemotherapy with BLM and CDDP for potential use in preclinical and clinical studies on colorectal carcinoma.

Materials and methods

Cell line

Murine rectum carcinoma cells CMT-93 (American Type Culture Collection, USA) were grown in Dulbecco's Modified Eagle Medium (DMEM) with Glutamax (Gibco, Invitrogen, Paisley, UK), supplemented with 10% foetal calf serum (FCS) (Invitrogen, Paisley, UK) and gentamicin (30 μg/mL) (Gibco, Invitrogen, Paisley, UK). Cells were routinely subcultured twice a week and incubated in an atmosphere with 5% CO_2 at 37 °C.

Drugs

BLM (Blenamax) was obtained from Pharmachemie BV (Haarlem, the Netherlands) as a crystalline powder. BLM was dissolved in saline (0.9% NaCl) at a concentration 1.5 mg/mL. CDDP (Cisplatyl) was obtained from Aventis (Paris, France) as a crystalline powder. CDDP was dissolved in sterile H_2O at a concentration of 1 mg/mL (3.3 mM). For each experiment, a fresh solution of BLM or CDDP was prepared. The final concentrations of both BLM and CDDP were prepared in DMEM. BLM concentrations of 0.00001 μM to 1 μM and CDDP concentrations of 6.7 μM to 266.6 μM were used in the experiments.

Electrochemotherapy protocol

Confluent cell cultures were trypsinized, washed in DMEM with FCS for trypsin inactivation and once in electroporation buffer (125 mM saccharose; 10 mM K_2HPO_4; 2.5 mM KH_2PO_4; 2 mM $MgCl_2 \cdot 6H_20$) at 4 °C. The final cell suspension was prepared in electroporation buffer at 4 °C and a concentration of 22 x 10^6 cells/mL. For the clonogenic assay, 90 μL of final cell suspension was mixed with 10 μL of BLM or CDDP solution at different concentrations. 50 μL

of the mixture (1 x 10^6 cells) were placed between two parallel electrodes with a 2 mm gap in-between and subjected to eight square wave electric pulses with electric field intensity 1300 V/cm, pulse duration 100 μs and frequency 1 Hz. Electric pulses were generated by an in-house build electroporator (University of Ljubljana, Faculty of Electrical Engineering, Ljubljana, Slovenia). Another 50 μL of the mixture (1 x 10^6 cells) served as a control of CDDP treatment alone. After electroporation, cells were incubated at room temperature for 5 min, diluted in 2 mL of growth medium and then plated for clonogenic, caspase-3/7 activity, cell viability assays, and Giemsa staining.

Clonogenic assay

CMT-93 cells were plated at a concentration of 300 cells/dish for exposure to BLM alone and 1200 cells/dish for combination of electroporation and BLM, whereas 600 cells/dish were plated for both CDDP alone and a combination of electroporation and CDDP. After 9 and 10 days (BLM and CDDP, respectively) colonies were fixed, stained with crystal violet and counted. The survival curve for the electrochemotherapy-treated cells was normalised for the cytotoxicity of electric pulses treatment alone. The inhibitory concentration of each treatment that reduced cell survival to 50% (IC_{50}) was determined graphically in each experiment. The experiment was repeated three times in triplicates for both BLM and CDDP.

Apoptosis

Apoptosis was measured by caspase-3/7 activity that was evaluated using the Caspase-Glo 3/7 Assay (Promega, Madison, USA) according to the manufacturer's instructions. After the electrochemotherapy protocol, CMT-93 cells (1.5 x 10^4 cells/well) were seeded in a 96-well plate (TPP, Trasadingen, Switzerland) and incubated at 37°C. After 16 h, a solution of Caspase-Glo 3/7 substrate and buffer (ratio 20 : 1) (Promega, Madison, USA) was added to each well. Plates were further incubated at 37°C for 2 h and luminescence was measured at 1 s integration time using a microplate reader (Tecan, Salzburg, Austria). The experiment was repeated twice in quintuplicates. Caspase-3/7 activity was normalized to the number of viable cells (as determined by the cell viability assay). Caspase-3/7 fold induction was determined as the ratio between caspase-3/7 activity in treated and control cells.

Cell viability was evaluated using the CellTiter 96 Aqueous One Solution Cell Proliferation Assay (Promega, Madison, USA) according to the manufacturer's instructions. After the electrochemotherapy protocol, CMT-93 cells (1.5 x 10^4 cells/well) were seeded in a 96-well plate (TPP, Trasadingen, Switzerland) and incubated at 37°C. After 16 h, a solution of MTS with PMS (ratio 20 : 1) was added to each well. Plates were further incubated at 37°C for 2 h and absorbance was measured at 492 nm using a microplate reader (Tecan, Salzburg, Austria). The experiment was repeated three times in quintuplicates.

Necrosis

Necrosis was evaluated by morphological changes in cells stained with Giemsa. For Giemsa staining, CMT-93 cells (7 x 10^4 cells/well) were plated in chamber slides 5 min after electroporation. After 18 h, the medium was removed and cells were washed with PBS. Cells were fixed in cold methanol for 20 min and then washed under running water. Extra liquid was wiped away and Giemsa's azure eosin methylene blue solution (Merck, Darmstadt, Germany) was added to the slides for 20 min. After incubation, slides were washed under running

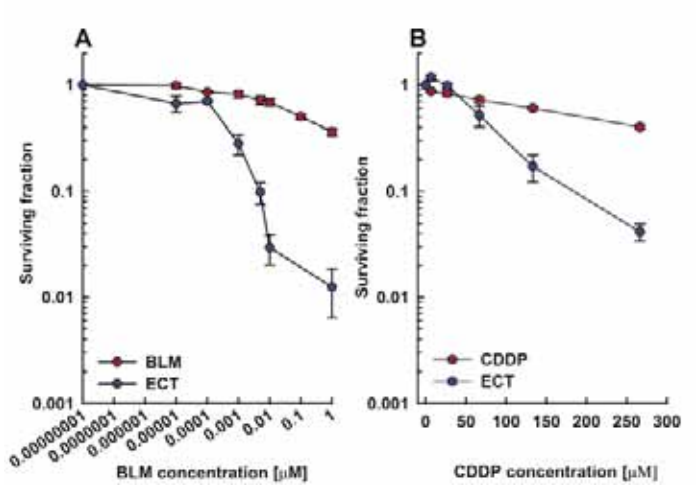

Figure 1. Potentiation of BLM and CDDP cytotoxicity *in vitro* by electroporation of CMT-93 cells. (A) Surviving fraction of CMT-93 cells after treatment with BLM alone or after electrochemotherapy with BLM. (B) Surviving fraction of CMT-93 cells after treatment with CDDP alone or after electrochemotherapy with CDDP.

water and air-dried. Samples were evaluated under a IX51 inverted microscope (Olympus, Tokyo, Japan). Photographs were taken with a CCD camera ColorView III (Soft Imaging System, Münster, Germany).

Results

Clonogenic assay

Exposure of CMT-93 cells to electric pulses resulted in an increase in both BLM and CDDP cytotoxicity (Figure 1). Throughout the range of BLM and CDDP concentrations investigated, cells exposed to either BLM or CDDP and electric pulses were more sensitive to the chemotherapeutics than those which were not exposed. The cells exposed to electric pulses were 2.8-fold more sensitive to CDDP as determined by the IC_{50} value. The cells exposed to electric pulses were 500-fold more sensitive to BLM as determined by the IC_{50} value. The surviving fraction of cells treated with electric pulses alone was 0.44 ± 0.04 (data not shown).

Apoptosis after electrochemotherapy with BLM

After BLM treatment, caspase-3/7 fold induction was significantly increased at 1 μM BLM in comparison to other tested concentrations ($p<0.05$). After electrochemotherapy with BLM, the caspase-3/7 fold induction was significantly increased both at 0.1 μM and 1 μM BLM. Interestingly, caspase-3/7 fold induction was higher at 0.1 μM BLM; however, the difference was not significant (Figure 2).

The cell viability in the range of tested BLM concentrations was decreased and it reached 73% at the highest tested BLM concentration. In comparison to control non-treated cells, cell viability is significantly reduced at 0.0001 μM BLM and higher ($p<0.05$). After electrochemotherapy with BLM, there was no significant difference in cell viability at low BLM concentrations (0.00001 μM - 0.01 μM). However, at 0.1 μM and 1 μM BLM, cell viability was significantly reduced in comparison to other tested concentrations. Interestingly, there was no significant difference in cell viability between these two concentrations (Figure 2).

Apoptosis after electrochemotherapy with CDDP

After CDDP treatment, the caspase-3/7 fold induction was significantly increased at 266.6 μM CDDP in comparison to other tested concentrations ($p<0.05$). After electrochemotherapy with CDDP, the caspase-3/7 fold induction was significantly increased at 133.3 μM and 266.6 μM CDDP ($p<0.05$). Caspase-3/7 fold induction was

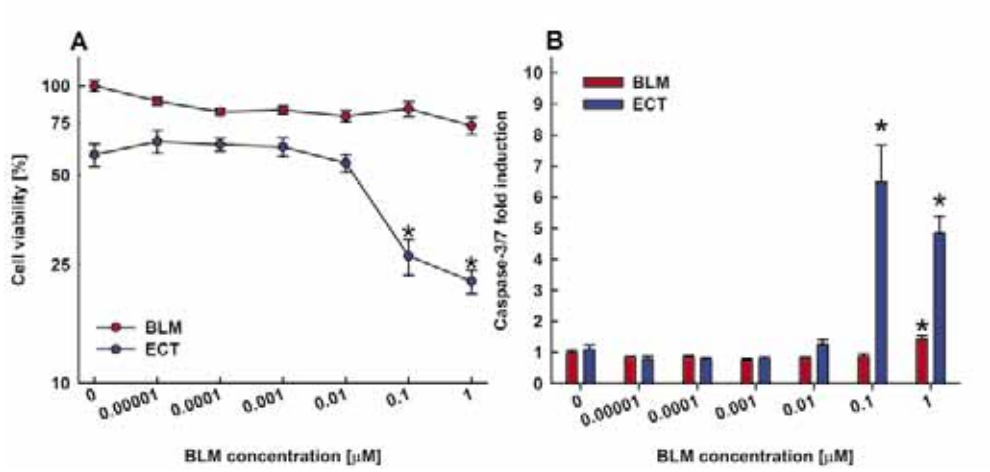

Figure 2. Cell viability (A) and caspase-3/7 fold induction (B) of CMT-93 cells after electrochemotherapy with BLM. Data are mean values pooled from two or three independent experiments. * p<0.05.

significantly higher at 266.6 μM than 133.3 μM CDDP (p<0.05) (Figure 3).

The cell viability in the range of tested CDDP concentrations was decreased and it reached 79% at the highest tested CDDP concentration. In comparison to control non-treated cells, cell viability after CDDP treatment was significantly reduced only at 133.3 μM and 266.6 μM CDDP (p<0.05). Interestingly, a significantly decreased cell viability was observed at 266.6 μM CDDP in comparison to other tested concentrations (p<0.05), but not to 133.3 μM. After electrochemotherapy with CDDP, cell viability was significantly reduced at 266.6 μM in comparison to all other tested concentrations (p<0.05) (Figure 3).

Necrosis after electrochemotherapy with BLM or CDDP

Cells were stained with Giemsa to evaluate the effect of BLM or CDDP treatment or electrochemotherapy with BLM or CDDP on cell morphology, specifically to determine necrosis. CMT-93 cells displayed

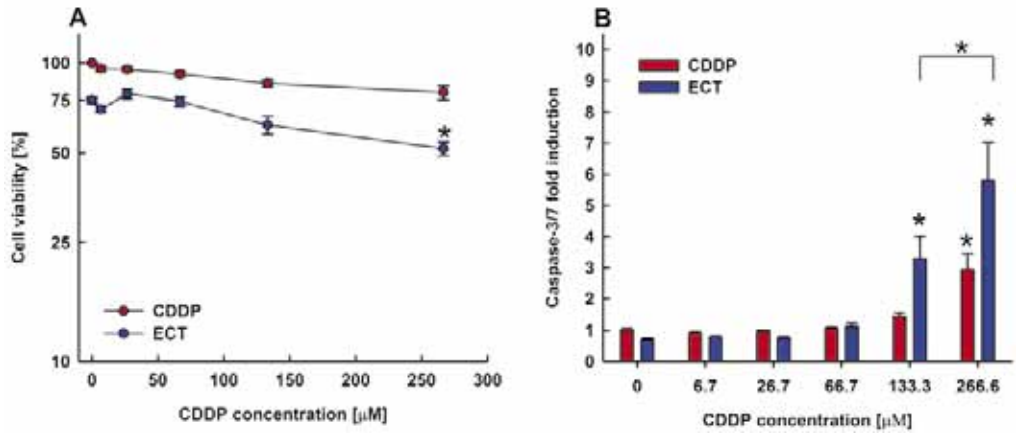

Figure 3. Cell viability (A) and caspase-3/7 fold induction (B) of CMT-93 cells after electrochemotherapy with CDDP. Data are mean values pooled from two or three independent experiments. * p<0.05.

Table 1. IC_{50} values of CMT-93 cell line treated with either BLM or CDDP with (+EP) or without (-EP) electroporation

	IC50		
drug	- EP	+ EP	*fold increase*
BLM	0.1 μM	0.0002 μM	500
CDDP	192.7 μM	68.3 μM	2.8

Table 2. The range of IC_{50} values of different human and murine tumour cell lines treated with either BLM or CDDP with (+EP) or without (-EP) electroporation

	IC50	
drug	- EP	+ EP
BLM	0.1 - 500 μM	0.0002 – 4.3 μM
CDDP	0.83 – 1000 μM	0.083 – 106 μM

typical epithelial morphology. The effect of electric pulses on cell morphology was only minor; some cells were enlarged and only a few cells displayed morphological characteristics typical for apoptotic or necrotic cell death. However, morphological changes progressively increased with increasing BLM or CDDP concentrations and also after electrochemotherapy. After treatment with higher BLM or CDDP concentrations, changes in cell size and shape were observed in comparison to control non-treated cells. Cells were enlarged, some were also multinucleated, and cytoplasm was vacuolarized. Apoptotic bodies, piknosis, karyorrhexis, and karyolysis, were also observed in comparison to control cells indicating necrotic cell death. These changes were more evident at higher concentrations of BLM or CDDP. On the other hand, after electrochemotherapy with BLM or CDDP the above-mentioned morphological changes were already observed at lower BLM or CDDP concentrations (Figure 4).

Discussion

In this study, we demonstrated the effectiveness of electrochemotherapy with BLM or CDDP on the CMT-93 colorectal carcinoma cell line. The exposure of cells to electric pulses enhanced cytotoxicity of both BLM and CDDP. Reduced cell viability was due to apoptotic and necrotic cell death. Furthermore, electrochemotherapy with BLM was more cytotoxic than electrochemotherapy with CDDP in CMT-93 colorectal carcinoma cells.

Our results demonstrate enhanced cytotoxicity of both chemotherapeutic drugs after electrochemotherapy. After exposure of the CMT-93 cell line to a combination of electric pulses and the chemotherapeutic drug, the cells were 2.8-fold more sensitive to CDDP and 500-fold more sensitive to BLM in comparison to exposure to the drug alone. A similar study also tested susceptibility of colorectal carcinoma cell lines Colorectal 26 and MC38 to electrochemotherapy. It demonstrated that these cells were much more sensitive to BLM cytotoxicity. Furthermore, cytotoxicity potentiation was significant only for BLM, but not for CDDP treatment.[9]

Previously, IC_{50} values (Table 2) were determined for different human and murine tumour cell lines for treatment with BLM or CDDP alone or in combination with electroporation.[3,6,9,11-13] Compared to these studies, CMT-93 cells appear more resistant to CDDP then other cell lines, even after electroporation, although electroporation significantly increased sensitivity to CDDP. CMT-93 cells were more sensitive to BLM, and after electroporation, cytotoxicity was potentiated 500-fold. Our results are also in agreement with the previously reported fact that electroporation of cells potentiates BLM cytotoxicity up to several thousand-fold, whereas CDDP cytotoxicity is potentiated up to 80-fold.[14]

The difference between enhancement of BLM and CDDP cytotoxicity can be as-

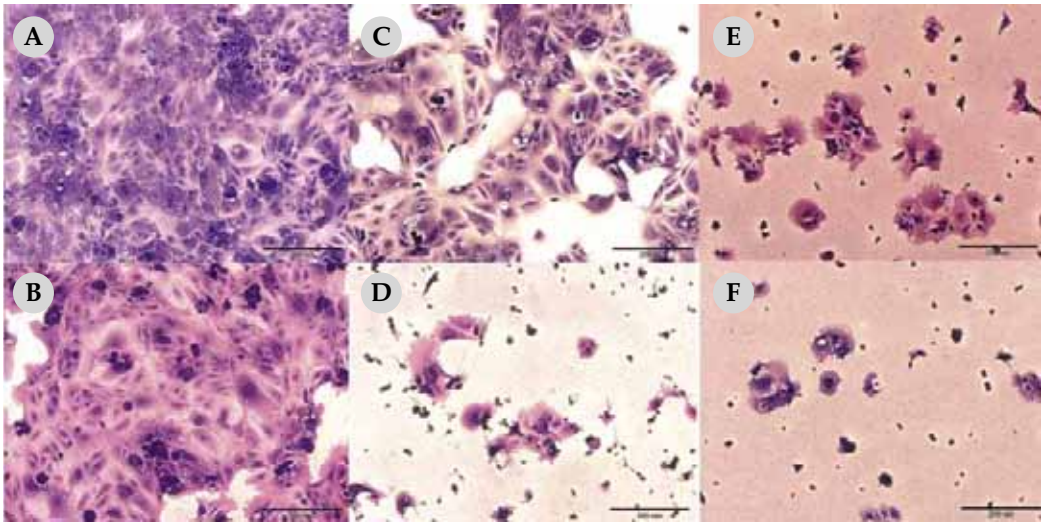

Figure 4. Changes in cell morphology were determined with Giemsa staining. (A) Control non-treated CMT-93 cells. (B) Cells exposed to electric pulses only. (C) Cells exposed to 1 μM BLM. (D) Cells exposed to electrochemotherapy with 1 μM BLM. (E) Cells exposed to 266.6 μM CDDP. (F) Cells exposed to electrochemotherapy with 266.6 μM CDDP.

cribed to the uptake of the drugs and also intracellular action of these drugs. Namely, the plasma membrane limits both BLM and CDDP uptake in the cells, as they cannot freely diffuse through the membrane. CDDP is a small inorganic molecule that enters the cells to some extent by passive diffusion and also by active transport via carrier molecules.[15,16] However, the overall flux across the membrane is limited. On the other hand, BLM is a complex organic molecule, and as such cannot diffuse freely across the plasma membrane.[17] The exact mechanism of its uptake is not known, however, involvement of receptor proteins on the plasma membrane is indicated.[18]

DNA is the main intracellular target of both BLM and CDDP. However, the mechanism of their cytotoxicity differs. CDDP interacts with DNA to form DNA-protein and DNA-DNA crosslinks.[19] On the other hand, BLM induces single- and double-strand DNA breaks.[20] When DNA damage, induced by either CDDP or BLM, exceeds the threshold level, cell death is triggered. The primary cytotoxic mechanism of DNA-damaging antitumour drugs may be induction of apoptosis. However, other types of cell death can occur in cell cultures exposed to the same drug. Individual cell death after BLM or CDDP exposure might be determined by several factors. It is dependent on drug concentration, the availability of energy and the metabolic condition of the cell.[15,21,22] BLM-induced DNA damage can trigger the apoptotic, pseudoapoptotic or mitotic cell death pathway. At low BLM concentrations, cells die of mitotic cell death, at intermediate BLM concentrations apoptosis is induced, whereas at high BLM concentrations, an apoptosis-like process takes place.[20,23] Also, apoptosis, necrosis, and mitotic cell death have been found in the same population of CDDP-treated cells.[21,24] At high CDDP concentrations (800 μM), cells undergo necrotic cell death over a few hours after treatment, whereas at low CDDP concentration (8 μM) cells undergo apoptosis following exposure to the drug over several days.[22]

Apoptosis is a mode of cell death characterized by unique morphological and bio-

chemical features. These include loss of cell-cell contact, cell shrinkage and blebbing, recognition by phagocytic cells, condensation and fragmentation of the nucleus, dependence on the energy supplied by ATP, and active protein synthesis.[21,25] Apoptosis results from activation of the caspase family of aspartate-specific proteases. Upstream caspases are activated early in the apoptotic process and they activate downstream caspases, such as caspase-3 and -7. These caspases are largely responsible for the cleavage of many other cellular proteins, leading to apoptosis.[21] Measurements of caspase-3 and caspase-7 activity can be used to detect apoptosis in cell cultures.

Since caspase activation is dependant on metabolic activity of the cell, the cell viability assay and caspase-3/7 activity assay were used to evaluate cell death pathway after electrochemotherapy. Cell viability and caspase-3/7 activity were determined 16 hours after electrochemotherapy, and caspase-3/7 activity was normalized to the number of viable cells. Only cells with an active metabolism can produce ATP and form a caspase activation complex, leading to activation of executioner caspases-3 and -7. Our study demonstrated decreased cell viability after exposure to BLM or CDDP. However, loss of cell viability was more prominent at high concentrations. Cell viability was further decreased after electrochemotherapy. The effect was more pronounced after electrochemotherapy with BLM than CDDP. Furthermore, electrochemotherapy with either BLM or CDDP activated caspases-3 and -7. However, the caspase-3/7 fold induction was significantly increased only at the highest concentrations of BLM and CDDP used.

Our results suggest that at low BLM concentrations, cells die after a few cell cycles in a caspase-independent slow cell death process and are in agreement with already demonstrated results that at a BLM concentration of 10 nM and below cells die slowly through a mitotic cell death.[23] Our results further demonstrated that at the highest tested BLM concentrations (0.1 μM and 1 μM), caspase-3/7 activation is apparent and this leads to the conclusion that apoptosis is triggered. The highest concentrations used are too low to induce excessive DNA damage that would lead to rapid cell death. However, DNA damage seems sufficient to activate executioner caspases and apoptosis.

After electrochemotherapy with CDDP, cell viability was significantly reduced at 266.6 μM and significant caspase-3/7 fold induction was seen at 133.3 μM and 266.6 μM. This indicates that apoptosis is triggered at these high concentrations. Similarly to BLM, at low CDDP concentrations, cells were metabolically active and caspase-3/7 fold induction was not significantly increased. Also, it was previously demonstrated that at low CDDP concentrations (8 μM) cells die of apoptotic death over several days.[22] In our experiments, caspase-3/7 activity was measured 16 hours after electrochemotherapy, which is too short a time to induce enough DNA damage to induce apoptosis at these low concentrations.

Although caspase-3/7 activation was significant at high concentrations, not all cells underwent apoptosis. Morphological changes observed after treatment with BLM or CDDP or electrochemotherapy with BLM or CDDP were the presence of apoptotic bodies, piknosis, karyorrhexis, and karyolysis. On the one hand, apoptotic bodies, piknosis and karyorrhexis are hallmarks of apoptosis, whereas on the other hand, karyolysis is typical for necrotic cells. Our results demonstrated that cells died of either apoptotic or necrotic cell death after electrochemotherapy with BLM or CDDP. Necrotic cells were more abundant at higher BLM or CDDP concentrations, especially after electrochemotherapy. These results

are in agreement with cell viability and the caspase-3/7 activity assay. However, reduced cell viability at high BLM or CDDP concentrations after electrochemotherapy was not only due to apoptosis, but also due to necrosis which resulted in pronounced reduction of the cell's clonogenic potential.

To conclude, our study confirmed that CMT-93 colorectal carcinoma cells are sensitive to electrochemotherapy with both BLM and CDDP. To apply electrochemotherapy to the treatment of colorectal carcinoma, special electrodes that allow delivery of electric pulses to more deep-seated tumours must be developed. Currently, electrode systems are under development for intra-luminal delivery by endoscopes, laparoscopic systems or intravascular catheters.[26] Further development of special electrodes will permit application of electrochemotherapy to the treatment of colorectal carcinoma for those patients that cannot undergo traditional treatment modalities due to severe complications.

Acknowledgements

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research article

Postoperative radiochemotherapy for gastric adenocarcinoma: long term results

Irena Oblak, Franc Anderluh, Vaneja Velenik

Department of Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background. *To analyze the efficacy of postoperative radiochemotherapy with 5-florouracil (5-FU) and leucovorin (LV) applied in the patients with gastric carcinoma treated in a single institution.*

Patients and methods. *Between 2001 and 2004, 123 patients with resected gastric adenocarcinoma were treated with postoperative concomitant radiochemotherapy with 5-FU and LV. The adjuvant treatment consisted of five cycles of chemotherapy with 5-FU (425mg/m^2 IV) and LV (20 mg/m^2 IV) and concomitant radiotherapy with the total dose of 45 Gy.*

Results. *The treatment was completed according to the protocol in 82% of patients. The frequency and severity of early toxic effects induced by radiochemotherapy were manageable. Median follow-up time of 56 survivors was 64.5 months (range: 51.7-96.4 months). The 5-year locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS) were 81%, 48.3%, 50.4%, and 48.4%, respectively. The multivariate analysis showed that the tumor involvement of cardia and low intensity of chemotherapy were independent adverse prognostic factors for DSS and OS. More advanced pT-stage and tumors with diffuse growth type according to Lauren were identified as negative independent prognostic factor for OS. They were also on the threshold of statistical significance for DSS.*

Conclusions. *Postoperative radiochemotherapy for gastric carcinoma has acceptable toxicity, and is effective particularly in regard to LRC. High incidence of distant metastases calls for more effective systemic regimens.*

Key words: gastric cancer; adjuvant therapy; radiochemotherapy; survival; toxicity

Introduction

In Slovenia as well as worldwide, gastric carcinoma is considered as a disease with poor prognosis. Radical surgery which can be performed in only 50-70% of patients[1,2] is a common treatment for localized disease. Long-term outcomes with surgery alone are still relatively poor because disease recurrence was observed in 75% of patients, and in 40-65% of them, the disease recurred

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Correspondence to: Assist. Prof. Irena Oblak, MD, PhD, Department of Radiotherapy, Institute of Oncology Ljubljana, Zaloška c. 2, 1000 Ljubljana, Slovenia. Phone: +386 1 5879 297; Fax: +386 1 5879 304; E-mail: ioblak@onko-i.si

Table 1. Pathohistological characteristics of tumors (n = 123)

Characteristics		No.	%
pT – stage	1	9	7.3
	2	39	31.7
	3	66	53.7
	4	9	7.3
pN – stage	0	4	3.3
	1	53	43.1
	2	42	34.1
	3	24	19.5
Overall stage	Ib	6	4.9
	II	26	21.1
	IIIa	37	30.1
	IIIb	24	19.5
	IV	30	24.4
Pathohistological tumor grade	1	5	4.1
	2	25	20.3
	3	87	70.7
	unknown	6	4.9
Bormann type	1	4	3.3
	2	14	11.4
	3	43	35
	4	24	19.5
	unknown	38	30.9
Growth type according to Lauren	diffuse	61	49.6
	intestinal	55	44.7
	unknown	7	5.7
Perineurial invasion	yes	59	48
	no	45	36.6
	unknown	19	15.4
Lymphovascular invasion	yes	66	53.7
	no	23	18.7
	unknown	34	27.6
Angioinvasion	yes	23	18.7
	no	45	36.6
	unknown	55	44.7

locally and/or regionally.[2-4] A number of studies have been conducted to improve the treatment outcome of these patients and, as a result, postoperative radiochemotherapy was established as a routine treatment in the USA as well as in other countries.[6-17] The authors believe that the INT 0116 protocol is safe and acceptable for clinical use.[3,5,8-11] Data on late side effects are scarce. It is suspected that the used radiation fields can cause the damage to the left kidney in some patients, resulting in hypertension and other renal problems.[17] Six months after radiochemotherapy for gastric cancer, Jansen *et al.* observed a 20% decrease in the function of the left kidney. They believe that the renal impairment may increase over time.[18]

In 2001, at the Institute of Oncology Ljubljana, Slovenia, postoperative radiochemotherapy was established as a standard clinical practice in the treatment of patients who had undergone radical resection of non-metastatic gastric adenocarcinoma of stages Ib-IV. The short-term results of this treatment regimen have already been published.[10] The aim of the present report is to present the long-term results of postoperative radiochemotherapy for gastric adenocarcinoma, including late treatment-related toxicity.

Patients and methods

Between 2001 and 2004, 123 patients (79 males, 44 females) with the mean age of 60 years (range: 31-76 years), were treated for gastric adenocarcinoma of TNM stages Ib-IV (nonmetastatic), with postoperative concomitant radiochemotherapy. One hundred and seven (87%) patients had radical resection (R0) of the tumor, and in the remaining 16 (13%) patients, non-radical (R1) resection was made. Distal subtotal, total,

and multivisceral resection of the stomach was performed in 40.7%, 29.3%, and 27.6% of patients, respectively, and three patients (2.4%) had resection of the carcinoma on gastric stump. In 92 (74.7%) patients, at least 15 lymph nodes were removed and histologically examined, in 27 (22%) patients, less than 15 lymph nodes were examined, while for 4 (3.3%) patients, no data on the lymph node status was available. Most frequently, the primary tumor originated in the antrum (38.2%). Sixty-one percent of patients had advanced disease and 96.7% of patients had N+ disease (Table 1).

After surgery, all patients with the disease of pathological stage Ib or more were presented to a multidisciplinary advisory team, consisting of a surgeon, radiation oncologist and medical oncologist, in order to assess the prospects of eventual adjuvant treatment. Eligibility of patients for adjuvant therapy was assessed with respect to the blood test results and performance status (≥2 according to the World Health Organisation [WHO]). More extensive radiologic investigations already performed before surgery to rule out metastatic disease, were repeated only in the patients with clinically suspected progression of the disease.

During the therapy, the patients were clinically examined and referred for hematological and biochemical blood testing once a week. The therapy-related local and systemic toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.[19] WHO scale was used to determine the performance status of patients and their body weight was measured on weekly basis.

Adjuvant treatment was initiated six weeks after surgery. It consisted of concomitantly applied chemotherapy and radiotherapy. In the chemotherapy part of the protocol, five cycles of 5-FU (425mg/m^2) and LV (20 mg/m^2) administered as five-day intravenous infusions were planned. The treatment cycle was repeated every 28 days. During radiotherapy, the intensity of chemotherapy was decreased. In the second and third cycle, only 4 and 3 applications of the drugs were administered, respectively. After the completed radiotherapy, the patients received two more five-day chemotherapy cycles.

Irradiation was applied during the second and third cycle of chemotherapy. The patients were irradiated on linear accelerator with 5-15 MV photon beams for 5 days per week, at a daily dose of 1.8 Gy. The irradiation field involved the primary tumor site and regional lymph node areas with a safety margin of 1.5-2 cm. Two opposite (AP-PA) beams were applied. Total irradiation dose was 45 Gy and total irradiation time 5 weeks.

After the completed treatment, follow-up examinations were performed every three months in the first two years and then at six month intervals to the end of five years. The patients were than referred back to their general practitioner's care and attended follow-up examinations only once per year. The follow-up examination consisted of clinical examination, complete blood count, liver and renal functional tests and measurements of CEA and Ca 19-9. Ultrasound (US) or computed tomography (CT) of the abdomen were performed every six months, chest radiography or CT once a year and endoscopic examination of the upper gastrointestinal tract as clinically indicated. During the follow-up period, any suspected disease relapse or recurrence was confirmed by biopsy.

Statistics

Statistical analysis was performed using personal computer and software statistical package SPSS, version 13 (SPSS Inc., USA).

Table 2. Toxicity of adjuvant radiochemotherapy

Toxicity	NCI grade (%)					
	0	1	2	3	4	Total
Stomatitis	48	10.6	15.4	26	0	100
Radiodermatitis	95.2	1.6	1.6	1.6	0	100
Diarrhoea	79.7	5.7	5.7	8.9	0	100
Dysphagia	44.7	12.1	21.2	22	0	100
Nausea, vomiting	56.9	11.4	13	18.7	0	100
Infection	50.4	18.7	18.7	12.2	0	100
Leukocyte count	30.1	29.3	30.1	9.7	0.8	100
Haemoglobin level	19.5	70.7	9.8	0	0	100
Platelet count	92.7	7.3	0	0	0	100

The main endpoints were as follows: locoregional control (LRC, the event was local and/or regional recurrence); disease-free survival (DFS, the event was local, regional or systemic recurrence); the disease-specific survival (DSS, the event was death due to gastric adenocarcinoma), and overall survival (OS, the event was death from any cause).

The survival of patients was computed from the date of surgery to the 1st of May, 2009 (close out date). Survival probability was calculated using Kaplan-Meier estimate[20], and log rank test[21] was used to evaluate the differences between individual groups of patients. Independent prognostic values of variables that appeared statistically significant on univariate analysis were tested by multivariate Cox regression analysis model.[22] Two-sided tests were used and the differences at $p < 0.05$ were considered as statistically significant.

Results

Treatment outcome

All 123 patients were evaluable for analysis. Postoperative chemotherapy started 3.6-11.9 weeks after surgery (median 5.9 weeks). Total postoperative treatment time ranged from 4.9- 32.6 weeks (median 17.6 weeks), whereas the duration of the radiotherapy part of the protocol ranged from 3.3-18 weeks (median 5.3 weeks). In regard to the intensity of radiotherapy and chemotherapy doses, 82% of patients completed the treatment according to the protocol. There was no treatment-related death. The frequency and severity of early toxic effects of radiochemotherapy are shown in Table 2. In regard to the late side effects, only renal functional impairment (the rise of creatinine level of grade 1, but without hypertension or other renal impairment) was observed in 5 patients (4.1%). The observed median time interval of creatinine level elevation was 10.5 months (range: 8.9-13.4 months).

On the close-out date, median follow-up time of all treated patients was 51.8 months (range: 5.3-96.4 months), with the median follow-up time of 64.5 months (range: 51.7-96.4 months) for 56 survivors. In 56 (45.5%) patients, alive at the time of analysis, 53 had no signs of disease. Of 67 (54.5%) dead patients, 60 died of gastric carcinoma, 4 of other causes (stroke, lung cancer, cancer of the *caecum*, myocardial infarction; 1/4 patients with simultaneous locoregional recurrence), and in 3 patients, the cause of death could not be determined.

After adjuvant radiochemotherapy, disease re-appeared in 62 (50.4%) patients. Local and/or regional recurrence developed in 7 (5.7%) patients in the median time of 18 months (range: 9.7-56.3 months) after surgery. Locoregional failure and systemic dissemination were diagnosed in 11 (8.9%) patients in the median time of 11 months (range: 6.2-25.7 months), and

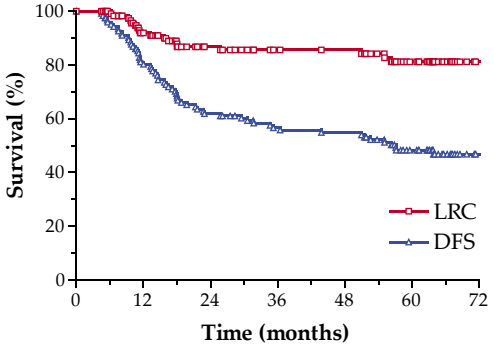

Figure 1. Locoregional control (LRC) and disease-free survival (DFS).

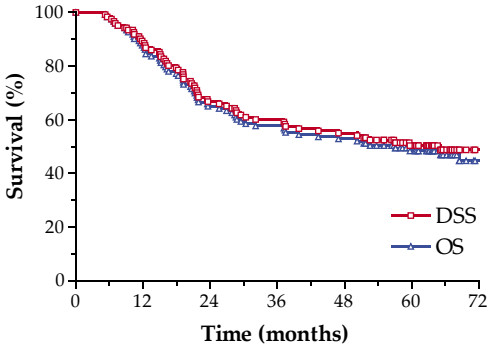

Figure 2. Disease-specific survival (DSS) and overall survival (OS).

systemic metastases alone in 44 (35.8%) patients in the median time of 16 months (range: 4.5-63.8 months). The 5-year LRC, DFS, DSS and OS were 81%, 48.3%, 50.4%, and 48.4%, respectively (Figures 1,2).

Prognostic factors

On univariate analysis of survival, locally advanced disease (pT3-4, pN3, overall TNM stage IV) was predictive for worse LRC and survival compared to early disease stages. In addition, poor outcome of patients was associated also with higher degree of stomach involvement with cancer (whole stomach vs. involvement of individual stomach areas), tumor location in the stomach (cardia vs. other subsites), Borrmann type 4, growth type according to Lauren (diffuse type vs. others), with the presence of vascular and perineurial invasion and intensity of chemotherapy (<5 cycles vs. 5 cycles of chemotherapy) (in all instances $p<0.05$).

The multivariate analysis showed that the tumor involvement of cardia and low intensity of chemotherapy were independent adverse prognostic factors for DSS and OS. More advanced pT-stage and tumors with diffuse growth type according to Lauren were identified as negative independent prognostic factor for OS. They were also on the threshold of statistical significance for DSS (Table 3).

Discussion

Short-term results of pooperative treatment with radiochemotherapy for gastric cancer in our population of patients have already been published.[10] As some other authors, we may also conclude that the combined radiotherapy and chemotherapy with 5-FU is feasible, with acceptable toxicity, and seems to have a potential to improve treatment outcome compared to surgery as the sole mode of treatment for this poor prognosis group of patients.[5-15] After a longer follow-up, excellent LRC and acceptable DFS, DSS and OS were confirmed, which concurs with the results from other studies.[5,6,8,9,11,13,23]

In the present analysis, the patients with more advanced tumors, cardia involvement, perineurial and vascular invasion had poorer survival. With the prolongation of follow-up time, the diffuse growth type according to Lauren, Borrmann type 4 and low number of chemotherapy cycles, were also recognized as negative prognostic factors for disease outcome. All these factors are considered to be well established negative prognosticators in clinics for patients

Table 3. Multivariate analysis of survival

Prognostic factors	n	Locoregional control	Disease free survival	Disease specific survival	Overall survival
		p	p	p	p
pT- stage					
pT 1+2	48			0.06	0.04
pT 3+4	75				
pN- stage					
pN 0+1+2	98				
pN 3	25				
Overall stage					
Stage Ib –III	93				
Stage IV	30				
Stomach involvement					
Whole stomach	7				
Individual areas	116				
Primary tumour site					
Cardia	16			0.01	0.01
Other sites	107				
Perineurial invasion					
Yes	45				
No	59				
Angioinvasion					
Yes	45				
No	23				
Borrman type					
Type 1-3	61				
Type 4	24				
Growth type according to Lauren					
Diffuse	61			0.09	0.05
Intestinal	56				
No of ChT cycles					
Less than 5 cycles	24			0.03	0.04
Five cycles	99				

pT – pathological T-stage; pN – pathological N-stage; ChT – chemotherapy.

with gastric cancer or with another malignancies and are also usually mentioned as such in pertinent literature.[4,24-27] The subgroup of patients with early, distal tumors in whom distal subtotal resection was performed had no better outcome compared to those who had more advanced disease and, consequently, underwent more extensive surgery. This observation pointed out the potential of adjuvant therapy to neutralize otherwise well established prognostic power of higher tumor stage and tumor's localization. Contrary to our previous analysis[10], the dose of 5-FU per cycle and pretreatment Hb concentration ≤110 g/l lost their influence on survival. The reason for this finding could be longer follow up and consecutively more adequate statistical analysis.

The results of both multivariate analyses (*i.e.* the one from the past and the present one) exposed tumors located in the cardia as negative and independent prognosticators, which was pointed out also in other similar studies.[26,27]

In the present analysis, like at the most of analysis of other malignancies[25], to no surprise, a more advanced pT-stage was established as negative independent prognostic factor for OS, while for DSS it was on the threshold of statistical significance. The patients who

received less than five cycles of chemotherapy had worse DSS and OS. It is well known that the intensity of chemotherapy can have an influence on treatment outcome neoplasma.[24,28] In our series of patients, we didn't notice other serious late toxicities than the rise of creatinine blood level of grade 1. Jansen *et al.* observed a progressive decrease in the function of the left kidney which was 11% and 52% after 6 and 18 months, respectively.[18] Due to the more accurate conformal radiotherapy planning, we hope there will be less late renal toxicity[29,30], however, to approve this, longer follow-up of our patients is needed.

Because of high incidence of unresectable disease and distant metastases, this issue is to be addressed in future prospective studies exploring new systemic drugs and regimens. We should pay greater attention to preoperative radiochemotherapy, which could be the best treatment approach also in this type of malignancy, as it is in rectal, esophageal and breast cancer[31], although more randomized trials are needed to evaluate the survival benefits of this approach.

Conclusions

From the analysis of the treatment results of a group of 123 patients with operable gastric carcinoma and median follow up time of almost 5 years (more than 5 years in survivors), we may conclude that postoperative adjuvant radiochemotherapy with 5-FU and LV can efficiently improve the treatment outcome, particularly in regard to LRC, with acceptable early and late toxicity. Because of high incidence of distant metastases, this issue has to be addressed in well designed future prospective studies exploring new systemic drugs and regimens.

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research article

Influence of surgical treatment and radiotherapy of the advanced intraoral cancers on complete blood count, body mass index, liver enzymes and leukocyte CD64 expression

Tadej Dovšak[1], Alojz Ihan[2], Vojislav Didanovič[1], Andrej Kansky[1], Nataša Ihan Hren[1]

[1]Clinical Department of Maxillofacial and Oral Surgery, University Medical Center, Ljubljana, Slovenia; [2]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia

Background. *The aim of our study was to evaluate the influence of the surgery and radiotherapy of the advanced oral squamous cell carcinoma on the complete blood count, body mass index (BMI), acute inflammatory response, liver enzymes and expression of the CD64 index on leukocytes in the peripheral blood.*

Patients and method. *Venous blood was obtained from 16 patients with advanced oral squamous cell carcinomas treated with radical surgery and external beam radiotherapy. Blood samples were collected prior to surgery (T1), after surgery (T2) and after radiotherapy (T3). Blood samples were analyzed for whole blood count, immunoglobulin G levels, liver enzymes (transaminases (ALT and AST) and gamma-glutamyl trasferase (γ-GT)), inflammatory response markers (C-reactive protein, erythrocyte sedimentation rate, albumin, white blood count, leukocyte count and CD64 expression on leukocytes). Assessment of nutrition was done by calculating the body mass index.*

Results. *Surgery caused anaemia, trombocytosis, leukocytosis, lymphopenia, rise in acute phase proteins, elevation of CD64 expression on monocytes and neutrophyls, elevation of liver transaminases and lowering of γ-GT, albumin, protein and bilirubin levels. After radiotherapy haemoglobin, leukocytes, C-reactive protein, erythrocyte sedimentation rate, liver transferases, albumin, bilirubin and proteins returned almost to T1 levels, levels of lymphocytes, γ-GT and body mass index lowered. IgG levels remained almost unchanged at T2 and T3. Levels of the CD64 expression on monocytes and neutrophyls also elevated after radiotherapy.*

Conclusions. *Surgery caused a significantly larger acute phase response than radiotherapy, while radiotherapy worsened the already present lymphopenia.*

Key words: intraoral cancer; surgery; radiotherapy; blood parameters

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Correspondence to: Tadej Dovšak, MD, Clinical Department of Maxillofacial and Oral Surgery, University Medical Center, Ljubljana, Slovenia; Phone: +386 1 522 4235; Fax: +386 1 522 2495; E mail: tadej.dovsak@kclj.si

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common neoplasm in the European Union.[1] Advanced OSCC is treated with surgery and then radiotherapy (RT) and/or chemotherapy.[2] Five year survival rates for patients with advanced OSCC are below 55%[3], so researchers are still searching for better treatment modalities. The single most important factor influencing the outcome of patients with squamous cell carcinomas (SCC) of the upper aerodigestive tract is like at the other malignancies the stage of the disease at the time of initial diagnosis and treatment.[4-6] Once the tumour is no longer localized but has disseminated to regional lymph nodes, the probability of 5 year survival reduces to nearly half.[7-9] The patient's long-time prognosis is also worsened by the fact that the new primary SCC of upper aerodigestive tract occurred in 20% of these patients.[10]

Surgical trauma produces alterations in the hemodynamic, metabolic and immune responses of patients in the postoperative period. This injury response is a dynamic process that follows a specific pattern that has been defined based on clinical and scientific observations.[11] The initial proinflammatory immune response or systemic inflammatory response syndrome (SIRS) is mediated primarily by the cells of innate immune system. This is followed by a compensatory anti-inflammatory or immunosuppressive phenotype that is mediated primarily by cells of the adaptive immune system, which predisposes the host to septic complications[9] and may be also promotes the tumour growth and metastases.[13,14] Cell mediated immunity is suppressed for several days after surgery and more invasive procedures lead to deeper and longer immunosuppression.[14,15]

The role of RT for OSCC treatment is well established; modern equipment and techniques have minimized morbidity.[16] Toxicity is related to site and dose; acute toxicity is related to the inflammatory process induced within the radiation field. These effects occur to some degree in the majority of patients, but they are self-limited in duration. The presence of late toxicity is determined by the total dose of radiation given and not by the daily dose or fraction size.[17-19] Although lymphocytes are highly sensitive to radiation damage[19,20] this toxicity is not usually assessed.

The aim of our study was to evaluate the effect of major surgical procedures and RT of advanced OSCC on the complete blood count, body mass index (BMI), acute inflammatory response, liver enzymes and expression of the CD64 index on leukocytes in the peripheral blood by the prospective non-randomized study.

Patients and methods

Our prospective non-randomized study was running from 2007 to 2009 on the Clinical Department for Oral and Maxillofacial Surgery, University Clinical Center in Ljubljana. Sixteen patients with advanced OSCC were selected. The study group included 12 men and 4 women with median age 61 years (range 42-80 years). All were Stage III and IV according to the American Joint Committee on Cancer staging.[21] Inclusion criteria were that surgery and radiotherapy were the only treatment modalities. The local Ethics Committee of the Republic of Slovenia ensured that research protocol and appropriate written consent was obtained from each patient.

Blood samples T1 were collected between 1 to 17 days before surgery (mean ± SD; 8.9 ± 5.9). All patients were surgically treated with *en bloc* excision of tumour and modified neck dissection (five of them with bilateral) and subsequent re-

construction with flaps (9 with free flaps: 6 radial forearm, 1 iliac crest, 1 anterior lateral thigh, 1 fibula; 3 with pedicled flaps: 2 pectoralis major muscle, 1 temporalis muscle). Median blood loss during operation was 430 ml (range 200-1000 ml) which was assessed by the anaesthesiologist and surgeon. In all but one patient, temporary tracheotomy was performed at the time of operation. All patients had confirmed clear margins with frozen sections at the time of operation. In one patient, revision of the operative field was required immediately after operation because of haemorrhage. All free flaps were viable and functioning. The tracheotomy tube was removed at median day 6 (range 3-15). All patients were fed by nasogastric tubes (NGTs) for the median time of 9 days (range 5-15). Six patients received postoperative transfusion of concentrated erythrocytes for the correction of haemoglobin levels bellow 90 mg/l. All patients were treated with antibiotics for the median time of 8 days (range 5-10). Blood samples T2 were taken between 8 and 26 days after surgery (mean ± SD: 15.4 ± 4.4).

Patients were irradiated with an external beam on the 6 MV linear accelerator. They received between 58 and 66 Gy (mean ± SD: 60.5 ± 1.9), divided on 2 Gy daily fractions, five times a week. This RT was applied within 6 weeks after the surgery. No patient received hyperfractionated RT or chemotherapy. Blood samples T3 have been collected from 28 days up to 128 days post-RT (mean ± SD: 56.6 ± 36.9).

At the time of blood sampling all patients were weighted and their height was measured at T1. These measures were used to calculate body mass index (BMI, kg/m^2).

Blood sampling

The blood samples were taken from the cubital vein. 1 EDTA-containing test tube (5 ml) of peripheral blood was obtained for haematological, biochemical and cytometrical laboratory tests.

Expression of CD64 on neutrophils and monocytes

Expression of CD64 on neutrophils, monocytes and lymphocytes was measured by quantitative flow cytometry with a FACSCalibur flow cytometer (Becton Dickinson, NY, USA) and FACSCanto flow cytometer (Becton Dickinson, CD, USA) using the Leuko64TM assay (Trillium Diagnostics, LLC, Maine, USA). The assay is for research use only and is composed of three antibodies with specificities to CD64 (clones 22 and 32.2, both fluorescein isothiocyanate (FITC) conjugated) and a fluorescence bead suspension with three fluorescence signals (green fluorescence due to FITC, orange fluorescence similar to PE and red fluorescence of starfire red) for unique identification of beads, and used for instrument calibration and standardization of leukocyte CD64 expression in human blood. The sample preparation and flow cytometer setup were based on the manufacturer's instructions. Briefly, 50 μL of whole blood, or diluted whole blood to adjust leukocyte concentration to less than 25 x109 /L, was incubated for 15 minutes in the dark at room temperature with a mixture of murine monoclonal antibodies followed by red cell lyses with an ammonium-chloride-based solution (Trillium Lyse). Fluorescence beads were then added and flow cytometer analysis was performed on a minimum of 50,000 leukocytes. Data analysis for fluorescence intensity was performed by CellQuest software (Becton Dickinson, CA, USA). MFI was measured as a linearized value of log scale on monocytes (green, positive control, measuring CD64 expression), neutrophils (blue, measuring CD64 expression), and beads (aqua blue, measuring FITC and PE expres-

Table 1. Median values; SD of leukocytes, platelets, neutrophils and lymphocytes (10*9/L), erythrocytes (10*12/L) and Hb levels (g/L) in observed times (before surgery (T1) and after surgery (T2); after RT – T3) and their normal values. The significant differences ($p<0.05$) according to the preceding value are marked by *

Blood	T1	T2	T3	Normal values
Leu (10*9/L)	8.37 (3.7)	9.06 (2.9)	7.16 (2.3)*	4.0-10.0
Erci (10*12/L)	4.16 (0.7)	3.73 (0.5)*	4.33 (0.4)*	4.20-6.30
Hb (g/L)	138.38 (14,2)	119.06 (10.9)*	134.31 (13.8)*	120-180
Pt (10*9/L)	248 (94)	466 (180)*	279 (79)*	140-340
Neutr (10/9/L)	5.1 (2.7)	6.2 (2.5)*	5.1 (2.0)*	1.6-7.5
Lym (10*9/L)	2.10 (0.8)	1.96 (0.7)	1.13 (0.6)*	1.4-3.3

Legend: Leu - leukocytes; Erci - erythrocytes; Hb - haemoglobin; Pt - platelets; Neutr - neutrophils; Lym - lymphocytes

sion). Index calculation was performed by Leuko64 QuantiCalc software (Trillium Diagnostics, Main, USA). Index measurements were derived by the ratio of linearized MFI of the cell population to the FITC signal from the beads. An internal negative control of the assay was provided by the automated measurement of the lymphocyte CD64 index, which had to be less than 1.0, and an internal positive control of the assay was provided by automated measurement of the monocyte CD64 index, which had to be more than 3.0. Flow cytometry was performed up to 36 hours after blood sampling. Before the beginning of the study, the influence of delayed sample analysis was done and no significant difference in levels of CD64 expression was detected in the first 36 hours after blood sampling. Isotype-control antibodies were routinely used in each experiment to detect non-specific staining; however the calculation of CD64 MFI was done without subtracting isotype-control MFI in order to accurately compare the ratio (index) of linearized MFI to MFI alone.

Statistics

Data were presented as the median and 95% confidence interval of the mean. Comparison between groups was made using the unpaired Mann-Whitney test and analysis of variance (ANOVA). Proportions of patients

Table 2. Median values, SD of BMI (kg/m2), levels of proteins, albumin, IgG (g/L), bilirubin (μmol/L), ALT, AST and γ-GT (μkat/L) in observed times. The significant differences ($p<0.05$) according to the preceding value are marked by *

Nutrition&Liver	T1	T2	T3	Normal values
BMI (kg/m2)	23.03 (4.8)	22.18 (4.8)*	21.11 (4.6)*	19-25
Proteins (g/L)	73.56 (5.5)	71.94 (4.4)	75.88 (4.6)*	65-80
Albumin (g/L)	41.94 (4.8)	38.81 (3.2)*	42.06 (4.9)*	32-55
IgG (g/L)	12.46 (3.7)	12.15 (2.3)	12.78 (2.6)	6.90 – 14.00
Bilirubin (μmol/L)	13.19 (7.1)	6.75 (2.7)*	10.19 (5.2)*	<17
AST (μkat/L)	0.53 (0.3)	0.58 (0.4)	0.43 (0.3)	<0.58
ALT (μkat/L)	0.35 (0.1)	0.69 (0.5)*	0.42 (0.3)*	<0.74
γ -GT (μkat/L)	164 (2.7)	1.34 (1.0)	0.52 (0.3)*	<0.92

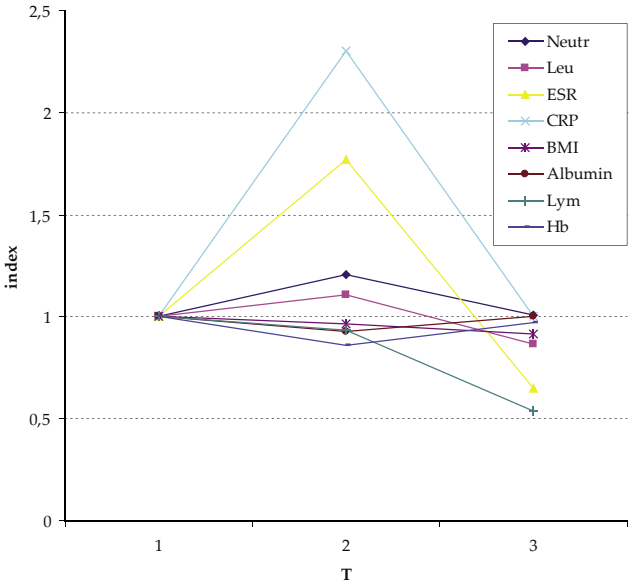

Figure 1. The average values of neutrophils, leukocytes, ESR, CRP, BMI, albumin, lymphocytes and haemoglobin are indexed on T1 value. Only the T2 values of leukocytes and lymphocytes did not reach the statistically significant level ($p<0.05$).

were compared by the $\chi 2$ test. The differences were considered to be statistically significant at the level of $p<0.05$. The statistical analysis was performed using Statistical Package for the Social Sciences for Windows, version 12.0 (SPSS Inc., Chicago, USA).

Results

Blood cell counts and Hb results are presented in Table 1 at T1, T2 and T3 with the normal values of these parameters in our referential laboratory.

Values of markers of nutrition and liver enzymes at sampling times are presented in Table 2 with the normal values of these parameters in our referential laboratory.

Results of values at T1, T2 and T3 of the acute phase proteins together with neutrophils, leukocytes and indexes of CD64 expression on the monocytes and neutrophils are presented in Table 3.

The advanced surgical procedures of OSSC had caused anemia, thrombocytosis, leukocytosis, lymphopenia, rise in acute phase proteins (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), elevation of CD64 expression on monocytes and neutrophils, elevation of liver transaminases and lowering of γ-GT, albumin, protein and bilirubin levels. After RT, haemoglobin, leukocytes, ESR, CRP, liver transferases, albumin, bilirubin and proteins returned almost to T1 levels; levels of lymphocytes, γ-GT and BMI decreased (Figure 1). IgG levels remained almost unchanged at T2 and T3. Levels of the CD64 expression on monocytes and neutrophils also elevated after RT.

Discussion

The purpose of our study was to establish the systemic influences of the surgical treatment and RT for the OSSC. Our results showed that advanced surgical procedures of OSSC caused a significantly larger acute phase response than radiotherapy, while radiotherapy worsened the already present lymphopenia. IgG levels remained almost unchanged at T2 and T3. Levels of the CD64 expression on monocytes and neutrophils also elevated after RT.

The postsurgical anaemia observed in our patients has been expected. During major surgery on the head and neck substantial blood loss may occur, varying between mean values of 500-1500 ml.[22,23] This results in a lower haemoglobin level after surgery and thus before radiotherapy, in particular when the haemoglobin level is

Table 3. Median values and SD of the markers of inflammatory response (leukocytes, neutrophils, ESR, CRP, indexes of CD64 on monocytes and neutrophils) at T1, T2 and T3. The significant differences (p<0.05) according to the preceding value are marked by *

Inflammation	T1	T2	T3	Normal values
Leu (10*9/L)	8.37 (3.7)	9.06 (2.9)	77.16 (2.3)*	4.0-10.0
Neutr (10/9/lL)	5.1 (2.7)	6.2 (2.5)*	5.1 (2.0)*	1.6-7.5
ESR (mm/h)	33 (24)	58 (21)*	37 (18)*	<15
CRP (mg/L)	5 (6)	11.5 (18)*	5 (52)*	<5
iCD64 mono.	6.67 (1.0)	7.92 (1.9)*	8.67 (5.7)*	4.34-8.70
iCD64 neutr.	0.64 (0.1)	0.75 (0.2)*	0.95 (0.6)*	0.45-2.16

Legend: Leu - leukocytes; Neutr - neutrophils; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; iCD64 mono-index of CD64 expression on monocytes; iCD64 neutr - index of CD64 expression on neutrophils

kept relatively low to prevent thrombosis in a microvascular free flap reconstruction.[24] Anaemia is considered to be associated with hypoxia[21] resulting in worse clinical outcome as tumour hypoxia decreases the efficacy of radiation therapy as a result of decreased radiosensitivity[26-28] and because hypoxia itself may induce genetic alterations that are associated with worse outcome.[29] The blood loss in our study was low but still moderate anaemia developed. The cut off point of haemoglobin for transfusion used in our department is 90 g/l and 6 of patients were therefore given blood transfusion postoperatively. Blood transfusion is known to have some immunomodulatory effect[30] that might predict outcome.[31,32] Studies regarding anaemia prior to RT have sown that anaemic patients have lower locoregional control and lower overall survival.[27,33-35] Proposed levels of Hb prior to RT is 120 g/l[36], which was also the level of haemoglobin in our study after surgery.

After surgery there was a statistically significant rise in the number of platelets that returned within normal limits after RT in our results. This reactive thrombocytosis is known to be triggered by tissue trauma and major surgical procedures.[37] In a recent study Lu *et al.* showed that preoperative thrombocytosis was an independent prognostic factor of shorter survival in OSCC.[38] In our study none of them had preoperative thrombocytosis.

Leukocytes and neutrophil levels at all observed times were within normal values, although neutrophil levels elevated postsurgically also indicating inflammatory response. IgG levels did not change during treatment and were within normal limits; it was reported that IgG levels are normal in OSCC[39] and treatment modalities do not affect IgG levels.[40]

Major surgery is also a cause of transient lymphocyte decline[41,42], that returns to normal levels 5-8 days after surgery.[43] Since all blood tests were taken 8 days after surgery, we did not observe any statistically significant changes in lymphocyte decline after surgery. A study done by Kuss *et al.* has shown that lymphopenia persisted for more than 2 years after surgical removal of the tumour (squamous cell carcinoma of the head and neck)[44], which is not consistent with our findings.

Irradiation of the areas with abandoned bone marrow causes severe lymphopenia.[45,46] But even irradiation of the limited anatomical areas such as neck can cause lymphopenia lasting over 2 years, especially regarding some subpopulations of T lymphocytes.[44,47,48] Also in our study, RT almost halved the levels of lymphocytes. With RT, vertebrae are mostly spared from irradiation; also, the thymus is not in the radiation field and most of the neck nodes are removed at the time of operation. Possible mechanisms to explain lymphopenia are damage to lymphocytes in large vessels, and lymphatics in the radiation field at the time of irradiation. Also in older patients, there

is a limited thymopoesis even more potentiated with liver insufficiency and poor nutrition.[48] A longer period of observation will be required to compare our results with the studies that have shown a long lasting decline of lymphocytes after RT.[48]

Acute phase proteins are a family of inflammatory proteins synthesized by the liver whose levels change in response to injury, infection and neoplasia. ESR has been routinely used in the diagnosis of infections for decades. CRP levels rise approximately 4 to 12 hours after surgery and peak at 24 to 72 hours. Subsequently, CRP levels remain elevated for nearly 2 weeks.[49] All forms of significant tissue damage triggers acute phase response as well as different types of cancer, especially, when they are extensive and metastastatic.[50] High levels of ESR have also been found to be evidence of cancer progression in different malignancies and were correlated with poor prognosis.[51] Studies reported the prognostic value of the preoperative CRP in oesophageal, gastric, ovarian and colorectal carcinomas.[52-54] Recently a study from Khandavilli *et al.* reported that increased preoperative CRP was associated with worse overall survival in patients with OSCC.[55] In our study mean CRP levels at T1 were at the upper border of the normal range and in only three patients it was higher. By expanding the study and by enrolling more patients it would be interesting to compare patients with high CRP levels to their chances of overall survival. Results of levels of ESR and CRP showed that surgery caused a significant increase in the levels of ESR and CRP, and that at T3, levels returned almost to T1 levels. ESR levels were elevated even before surgery which is consistent with findings that acute and subacute changes of the ESR are most commonly due to malignancy, infection or inflammatory process.[56,57] Tang *et al.* also found no increase of CRP after RT in patients with cervical carcinoma[58] while some studies reported on considerably elevated levels after RT in patients with head and neck carcinomas and cervical cancer.[59,60] One of the reasons why levels of CRP and ESR levels returned to T1 levels after RT in our study is that blood samples at T3 were taken from 28 to 128 days after RT and in the above mentioned studies immediately after RT.

CD64 is a high-affinity and restricted isotype-specificity FcγRI receptor expressed on macrophages, monocytes, neutrophils, and eosinophils.[61] During bacterial infections, however, the neutrophil expression of CD64 is markedly increased.[63-65] Studies have confirmed that the level of CD64 expression is significantly higher in patients with infectious SIRS as compared to patients with noninfectious SIRS as well as adults and children.[66,67] All the indexes in our group were within the normal range, although surgery is known to elevate the levels of CD64 expression on monocytes and neutrophils.[68,69] The reason for this is due to the fast kinetics of these indexes making them useful for detecting bacterial infections and monitoring response to treatment. Levels declined 3 days after surgery[69] and all of our T2 blood samples were taken after day 3. However, there was a steady incline in indexes, which might be due to the increased microorganism invasion, most probably from the gut mucosa.

BMI in our patients steadily dropped throughout the course of the treatment (Table 2, Figure 1). Nieto *et al.* showed in their study that BMI lower than 22 for smokers and drinkers significantly increases odds ratio for developing oral cancer.[70] Since alcohol and tobacco abuse are the two most important etiological factors for OSSC[71], only 2 of our patients were nonsmokers and all admitted to drinking modestly. We decided to check BMI regularly in OSCC patients because of the known fact that cachexia-anorexia syndrome occurs in

30 to 80% of cancer patients.[72] Although BMI did not reach the malnutrition level it still points to the need of an even better nutritional support of these patients.

Conclusions

Because of the low survival rate of patients with OSCC, we decided to evaluate many parameters of these patients in a prospective study. We studied the influence of surgery and radiotherapy on our patients. The major surgical procedure had caused anaemia, thrombocytosis, leukocytosis, lymphopenia, rise in acute phase proteins, elevation of CD64 expression on monocytes and neutrophils, elevation of liver transaminases and lowering of γ-GT, albumin, protein and bilirubin levels. After radiotherapy, haemoglobin, leukocytes, C-reactive protein, erythrocyte sedimentation rate, liver transferases, albumin, bilirubin and protein levels returned almost to T1 levels; levels of lymphocytes, γ-GT and BMI decreased. IgG levels remained almost unchanged during the therapies. Surgery caused a significantly larger acute phase response than RT, while RT worsened the already present lymphopenia. Levels of CD64 expression on monocytes and neutrophils increased after RT.

The major influences of surgical procedures were transient and reactive, while those after RT caused a more profound and long lasting effects. The results obtained from our study are the starting points for further investigations of OSCC patients.

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research article

Quality of life in patients with cervical cancer FIGO IIb stage after concomitant chemoradiotherapy

Dzenita Ljuca[1], Goran Marosevic[2]

[1]Gynecology and Obstetrics Clinic, [2]Department of Radiotherapy, University Clinical Centre Tuzla, Bosnia and Herzegovina

Background. *The literature reports are unclear regarding the quality of life in patients after the concomitant chemoradiotherapy. Our aim was to define and compare the quality of life of patients with cervical cancer FIGO IIb stage before and after the concomitant chemoradiotherapy.*

Methods. *Nineteen patients were irradiated to 45 Gy in 25 fractions over 5 weeks to the pelvis and additional 20-24 Gy in 4-6 fractions were given by intracavitary high dosage rate (HDR) brachytherapy. Patients received 40 mg/m^2 of cisplatin once a week, starting from the first day of the intracavitary brachytherapy treatment, which is a total of 4-6 cycles of cisplatin. Patients were surveyed with two questionnaires for the assessment of the quality of life. They were developed by the European Organisation for Research and Treatment of Cancer (EORTC): one was cancer specific (EORTC QLQ-C30) and one was site specific (EORTC QLQ-Cx24). Patients answered the questions for the period immediately before diagnosed cervical cancer (thus being a control group) and for the period starting 12 months after the completion of the concomitant chemoradiotherapy (thus being an experimental group).*

Results*. A statistically significant difference between the median scores of these two groups has been found in the quality of life, role function, emotional function, social function, pain, fatigue and vaginal problems.*

Conclusions. *The quality of life of patients with cervical cancer FIGO IIb stage was better after concomitant chemoradiotherapy than before it.*

Key words: concomitant chemoradiotherapy; cervical cancer; quality of life

Introduction

Cervical cancer is a serious health problem since every year, around 500.000 women worldwide develop this disease.[1] It is a number one killer of young women in developing countries.[2] In 2007, in Bosnia and Herzegovina the incidence was 17/100.000 women. In the Federation of Bosnia and Herzegovina, most women with this disease are aged 45 to 54, with a smaller

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Correspondence to: Goran Marosevic, MD, Department of Radiotherapy, University Clinical Centre Tuzla, Trnovac bb, 75000 Tuzla, Bosnia and Herzegovina; Phone: +387 63 116 431; E-mail: mar.goran@hotmail.com

number of those aged 35 to 45. The disease prognosis of patients with cervical cancer depends on the stage of the disease at diagnosis.[3] The concomitant chemoradiotherapy is a gold standard in the treatment of locally advanced disease stages Ib-IVa, and it results in 5-year surviving rate of 65% for IIb stage.[4] The cervical cancer treatment is followed by early complications in the first 6 months after the completed radiotherapy and late complications after this period. The most frequent disorder after the combined treatment of cervical cancer by surgery and radiotherapy is urinary incontinence which limits the patient's activities, comfort and quality of life.[5] Late urinary toxicity after the whole pelvic radiotherapy is frequent also in patients with other cancers.[6] When evaluating the quality of life of patients with cervical cancer, it is important to monitor their mental status.[7] Patients who are disease free after radiotherapy of locally advanced, recurrent or persistent cervical cancer are at high risk of experiencing persistent sexual and vaginal problems compromising their sexual activity and satisfaction.[8] The above mentioned studies show that the cervical cancer therapy is followed by various complications which compromise the quality of life of those patients and it is lower than the one in the control group. However, all studies' control groups included healthy women from that geographical region and it resulted in the lower quality of life of women after the cervical cancer treatment, which was logical to expect. The control group for this study included the same women but in the period before the concomitant chemoradiotherapy which enables us to obtain the real impact of therapy to the quality of life of cervical cancer survivors. All this indicates that it is very important to study the parameters of the quality of life of patients with locally advanced cervical cancer in this way.

The aim of this study is to define and compare the quality of life of patients with cervical cancer FIGO IIb stage before and after the concomitant chemoradiotherapy.

Patients and methods

Patients

This retrospective-prospective study included patients in all age groups who were treated against cervical cancer FIGO IIb stage by the concomitant chemoradiotherapy. The research covered 19 patients. Patients answered the questions in the questionnaire for the period immediately before cervical cancer was diagnosed, thus creating a control group. Then they answered the questions in the questionnaire for the period of 12 months after the completion of the concomitant chemoradiotherapy, thus creating an experimental group. The answers were scored and by statistical data processing they were objectified in the form of results.

Including factors were: FIGO IIb stage of cervical cancer, patients treated by the concomitant chemoradiotherapy and patients with preserved cognitive functions.

Excluding factors were: other FIGO stages of cervical cancer, patients not treated by the concomitant chemoradiotherapy and patients with low cognitive functions.

The data about the patients treated against cervical cancer were taken from case histories and medical charts at the Gynaecology and Obstetrics Clinic of the University Clinical Centre Tuzla. They were treated in the period 2006-2008 at the Clinical Centre of Sarajevo University, at the Oncology Clinic. All patients were irradiated to 40-46 Gy of irradiation energy of 6 MV and 18 MV in 25 fractions over 5 weeks to the pelvis by the linear accelerator Siemens Primus and intracavitary brachytherapy dosage of 20-24

Table 1. EORTC QLQ-C30 mean and median functional scale and single - item scores before and after concomitant chemoradiotherapy

	Before (19 patients)	**After (19 patients)**			
Item	Mean (s.d.)	Median (range)	Mean (s.d.)	Median (range)	p
Global QOL	33 (25)	33 (0-100)	61(21)	66 (16-100)	<0.0001
Functional scale					
Physical function	76 (22)	87 (27-100)	77 (26)	87 (20-100)	0.26
Role function	57 (32)	34 (0-100)	74 (30)	84 (0-100)	0.04
Emotional function	54 (33)	42 (0-100)	80 (21)	92 (34-100)	<0.0009
Social function	80 (22)	84 (34-100)	90 (18)	100(34-100)	0.02
Cognitive function	94 (16)	100 (34-100)	98 (7)	100(67-100)	0.25
Symptom scale					
Pain	31(27)	33 (0-100)	14 (16)	16(0-50)	<0.005
Fatigue	44 (27)	44 (0-88)	23 (25)	13 (0-66)	<0.005
Nausea and vomiting	6 (17)	0 (O-66)	6 (14)	0 (0-50)	0.5
Single items					
Dyspnoea	26 (30)	33 (0-100)	19 (29)	0 (0-100)	0.13
Insomnia	34 (35)	33 (0-100)	24 (26)	33 (0-66)	0.13
Appetite loss	17 (27)	0 (0-66)	12 (19)	0 (0-66)	0.22
Constipation	29 (38)	0 (0-100)	24 (30)	0 (0-100)	0.34
Diarrhoea	8 (18)	0 (0-66)	8 (18)	0 (0-66)	0.5
Financial impact	34 (37)	33 (0-100)	40 (37)	33 (0-100)	0.13

Gy. Intracavitary brachytherapy was applied by a high dosage rate (HDR) with Ir192 by Varian Gammamed. Patients received 40 mg/m^2 of cisplatin once a week, starting from the first day of the intracavitary brachytherapy treatment, which is a total of 4-6 cycles of cisplatin. The concomitant chemoradiotherapy lasted 32 to 49 days in total.

Methods

Patients were surveyed with the questionnaires for the assessment of the quality of life EORTC QLQ-C30 and EORTC QLQ-Cx24. EORTC QLQ-C30 is widely use in oncology[9] and it is "the original questionnaire" which includes the scales of physical, emotional and social health of wide scale of cancer patients. This questionnaire includes five functional scales, three symptom scales for pain, fatigue, nausea and vomiting, a global health status quality of life scale and six single items for dyspnoea, insomnia, appetite loss, diarrhoea, constipation and financial impact. Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.[10] Greimel *et al.*[11] developed the EORTC QLQ-Cx24 questionnaire, modified for cervical cancer patients and it can be used only as a supplement to EORTC QLQ-C30. It includes 24 questions regarding the symptoms related to urinary and gastro-intestinal tract and vaginal problems and sexual activity of patients. They are grouped into 3 scales with multiitem scales and 5 single-item scales.

Statistical analysis

The scoring was performed according to the EORTC QLQ-C30 scoring manual.[10]

Table 2. EORTC QLQ-Cx24 mean and median functional scale and single – item scores before and after concomitant chemoradiotherapy

	Before (19 patients)		**After (19 patients)**		
Items	Mean (s.d.)	Median (range)	Mean (s.d.)	Median (range)	P
Functional scale					
Body image	85 (16)	84 (25-100)	88 (13)	92 (50-100)	0.33
Sexual functioning	34 (35)	48 (0-81)	35 (35)	48 (0-81)	0.28
Symptom scale					
Defecation problems	13 (16)	11 (0-55)	8 (13)	0 (0-44)	0.08
Micturition problems	25 (25)	16 (0-75)	23 (22)	25 (0-75)	0.35
L-S problems	34 (20)	22 (11-66)	31 (22)	33 (0-66)	0.27
Vaginal problems	43 (25)	55 (0-88)	6 (9)	0 (0-33)	<0.0001

The principle for scoring was to estimate the average of the items that contributed to the scale; this was the raw score. A linear transformation was used to standardise the raw score, so that scores ranged from 0 to 100. A high scale score represents a higher response level. The higher scale score for the functional scale or the global health status/QOL represents a higher level of functioning, or higher QOL; whereas the higher level of symptoms/problems for the symptom/item scales represents a higher level of symptomatology, or dysfunction. Missing values were calculated such that if at least one-half of the items from the scale had been completed, it was assumed that the missing items would have had values equal to the average of the items present.

Demographic and clinical data were calculated using descriptive statistics. Results of QOL information were expressed as means and medians. The nonparametric Wilcoxon signed ranks test was used to compare median scores of QOL scales between the examined groups of patients. A 5% level of statistical significance was used for variables ($p<0.05$). Data were analyzed using Arcus Quickstat Statistical Software (version 1.0.0.88, Medical Computing).

Results

The general results of QLQ-C30 for the patients before and after the concomitant chemo-radiotherapy are given in Table 1. The global quality of life scores, representing the overall health and quality of life of patients was statistically significantly better after the concomitant chemoradiotherapy than before it (33 *vs* 66; p<0,0001). The following was noticed: statistically significant improvement of emotional function (42 *vs* 92; p<0.0009), role function (34 *vs* 84; p=0.04) as well as better social function (84 *vs* 100; p=0.02). After the concomitant chemoradiotherapy, patients had significantly lower pain (33 *vs* 16; p<0.005) and fatigue (44 *vs* 13; p<0.005).

The results of QLQ-Cx24 for two analyzed groups are given in Table 2. Out of 19 patients monitored, 9 of them did not have sexual activities before and after the treatment. After the concomitant chemoradiotherapy, patients had significantly less vaginal problems (55 *vs* 6; p<0.0001). In functional scales and other symptom scales there was no statistically significant difference although they had less problems with defecation after the concomitant chemoradiotherapy (11 *vs* 8; p=0.08).

Discussion

Review studies indicate that the quality of life in cervical cancer survivors who were irradiated is worse compared to general female population, although definite conclusions have not been made, especially due to shortcomings of methodology.[12] This study examined the quality of life of the same patients before and after the concomitant chemoradiotherapy which enabled us to obtain the real information about the way this treatment affects the quality of life of patients. We are of the opinion that it is the reason why the results show that the quality of life is better after the concomitant chemo-radiotherapy.

Monitoring the quality of life in disease free period after radiotherapy should include the information about the treatment complications since it might help the patients deal with them and cure the disease symptoms.[6,13] It is important to monitor the mental status of cervical cancer patients in the assessment of their quality of life. While some studies indicate a low mental status with irradiated patients,[7,13] this study reveals significant improvements of emotional functions, higher role function and better social integration, which significantly affects a mental status. Due to tumour regression, pain and fatigue was significantly reduced in patients after the irradiation.

Studies indicate that disease-free patients after radiotherapy of locally advanced, recurrent or persistent cervical cancer, compared to general female population, are at high risk of experiencing persistent sexual function and satisfaction[8] and that the sexual dysfunction compromises the quality of life of cervical cancer survivors the most.[14] Our study does not indicate the difference in sexual function of surveyed patients since almost half of them did not have sexual activities before and after the irradiation due to issues not related to the disease itself. Some patients lost their sexual willingness or their husbands fear they might hurt them, while prior irradiation, they suffered from bleeding and pain during the intercourse, therefore, no differences in sexual function have been found. Since patients after the irradiation had significantly less vaginal problems regarding pain and bleeding, we assume that the sexual function should be better. These results clearly indicate that a doctor should discuss this problem with the future patients during the treatment, which would improve the quality of life of sexually active patients even more.

In conclusion, the quality of life in cervical patients FIGO IIb stage after the concomitant chemoradiotherapy is better than before it. The reason for this statement lies in the fact that pain and fatigue are reduced after the treatment and that emotional, role and vaginal functions are better.

The fact that there is no difference in the quality of sexual function in patients with cervical cancer after the concomitant chemoradiotherapy and that vaginal, social and emotional function are better, paths the way to a new research on this topic.

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Radiol Oncol 2009; 43(4): 213-224.

Paliativno zdravljenje bolečih kostnih zasevkov z obsevanjem

Gojkovič Horvat A, Kovač V, Strojan S

Izhodišča. Pri bolnikih z rakom je bolečina, ki jo povzročajo kostni zasevki, najpogostejši simptom, ki zahteva zdravljenje. Kostni zasevki pogosto predstavljajo prvi znak razširjene oblike bolezni. Najpogosteje jih povzročajo rak dojke, prostate in pljuč. Pri paliativnem zdravljenju je zelo pomembno, da dosežemo največji učinek s sorazmerno kratko in nezahtevno obravnavo. Namen takšnega zdravljenja je predvsem izboljšati kakovost bolnikovega življenja.

Zaključki. Boleče kostne zasevke zdravimo z analgetiki, področnim zdravljenjem (obsevanjem, kirurgijo) in sistemskim zdravljenjem (hormoni, kemoterapijo, drugimi zdravili, kot so bifosfonati ter radioizotopi). Velikokrat je potrebna multidisciplinarna obravnava. Najpomembnejše paliativno zdravljenje pri področni kostni bolečini ostaja obsevanje. V večini primerov je najprimernejše obsevanje z eno frakcijo, s katerim dosežemo dolgotrajni protibolečinski učinek. Zdravljenje moramo prilagoditi bolnikovemu kliničnemu stanju in pričakovani življenjski dobi.

Radiol Oncol 2009; 43(4): 225-232.

Budd-Chiarijev sindrom povezan z jetrno hidatidno cisto: retrospektivna analiza preiskav z barvnim dopplerskim ultrazvokom in s posebno pozornostjo na intrahepatalne venske obvodnice

Yilmaz C, Erkan N, Arslan M, Yildirim J, Kalaycioglu S

Izhodišča. Name retrospektivne raziskave je bil ovrednotiti preiskave z barvnim dopplerskim ultrazvokom pri bolnikih z Budd-Chiarijevim sindromom, ki je nastal zaradi hidatidne ciste v jetrih. Posebno pozornost smo namenili intrahepatalnim venskim obvodnicam.
Metode. Retrospektivno smo analizirali digitalne videoposnetke jeternih preiskav z barvnim Doppler ultrazvokom. Obravnavali smo 13 bolnikov z Budd-Chiarijevim sindromom.
Rezultati. Pri vseh bolnikih smo ugotovili vsaj en tip intrahepatnih venskih obvodnic, ki so bile značilne za Budd-Chiarijev sindrom. Vseh različnih tipov obvodnic je bilo 5: subkapsularne vene, vene v obliki vejice, ki so ponekod dajale vtis hokejske palice, pajkaste vene, fragmentirane vene in linearne vene. Razporejene so bile v neanatomskih oblikah. Najbolj pogoste obvodnice so bile v obliki vejice in smo jih našli pri 12 od 13 bolnikov (92,3%). Vsaj 2 različna tipa venskih obvodnic pa smo našli pri 8 od 13 bolnikov (61,5%). Z navadnim ultrazvokom nismo videli obvodnic pri 2 bolnikih, našli smo jih z barvnim Dopplerjem.
Zaključki. Budd-Chiarijev sindrom, ki je nastal zaradi hidatidne ciste v jetrih, lahko nepričakovano odkrijemo ob preiskavi bolnika z ultrazvokom. Poznavanje tipičnih ultrazvočnih slik intrahepatalnih venskih obvodnic omogoči ugotovitev pravilne diagnoze in hitro ustrezno zdravljenje. Priporočamo, da pri vsakem bolniku, ki ima hidatidne ciste, ne glede na klinično sliko naredimo preiskavo z barvnim dopplerskim ultrazvokom.

Radiol Oncol 2009; 43(4): 233-239.

Premikanje žilne opornice pri zdravljenju možganske anevrizme: prikaz dveh primerov

Pavlisa G, Ozretic D, Rados M, Pavlisa G

Izhodišča. Prikazujemo dva bolnika z akutno rupturirano kompleksno možgansko anevrizmo. Pri obeh bolnikih sta anevrizmi izhajali iz notranje karotidne arterije ob odcepišču zadnje komunikantne arterije.
Prikaz primerov. Anevrizmi sta imeli pri obeh bolnikih širok vrat, zato smo vstavili žilno opornico, ki je omogočila znotrajžilno zapiranje z vijačnico. Pri obeh bolnikih je prišlo do neželenega premika žilne opornice, vendar brez kliničnih zapletov. Anevrizmi smo uspešno zaprli z vijačnicami.
Zaključki. Na primerih takojšnjega zapiranja anevrizme po postavitvi žilne opornice v anatomsko zahtevnih lokacijah smo prikazali fleksibilnost žilne opornice z možnostjo njenega premika.

Radiol Oncol 2009; 43(4): 240-246.

Absces vratnih vretenc C1/C2 – napake v diagnostiki in zdravljenju

Stanković M, Marić D, Ilić M, Veselinović I, Ninković S, Sečen S

Izhodišča. Nespecifični osteomilitis zgornje vratne hrbtenice je zelo redek. Največkrat nastane zaradi širjenja vnetja *per continuitatem* iz bližnjega žarišča, manj pogost pa je vzrok hematogeno širjenje iz oddaljenega žarišča. Prikazujemo redek primer koagulaza negativnega stafilokoknega osteomilitisa vratnih vretenc, kjer je potek pogosto atipičen.
Prikaz primera. Analiziramo primer 57-letni bolnice, pri kateri ugotavljamo napačno diagnostiko ob subluksaciji atlasa na radiogramu vratne hrbtenice in zanemarjanje laboratorijskega izvida, ki je kazal na vnetje sečil. To je povzročilo napredovanje bolezni z nevrološko simptomatiko (tetraparezo). Načrtovali smo takojšen kirurški poseg v dveh delih – anteriorno dekompresijo in nato okcipitocervikalno fiksacijo obolelih segmentov, vendar je bolnica že po prvi operaciji umrla.
Zaključki. Zgodnje prepoznavanje znakov bolezni in čimprejšnja diagnoza sta nujna za pravočasno ustrezno zdravljenje. Dodatna destabilizacija prizadetega segmenta, ki smo jo povzročili s kirurško dekompresijo pri prvi operaciji (brez stabilizacije tega segmenta), lahko privede do smrtnega izida.

Radiol Oncol 2009; 43(4): 247-257.

Slikovna diagnostika pri bolnikih z rakom nazofarinksa: pomen preiskav z 18F FDG PET/CT v primerjavi s CT in MRI

Nordin AJ, Secondino S, Rahim NA, Pedrazzoli P, Siena S, Rossetti C, Aris T

Izhodišča. Namen raziskave je bil ovrednotiti klinično uporabnost 18F fluorodeoksiglikoza (FDG) PET/CT preiskave pri zdravljenju raka nazofarinksa v primerjavi z drugimi slikovnimi preiskavami.
Metode. Naredili smo retrospektivno raziskavo v bolnišnici Niguarda v Milanu. Analizirali smo 24 bolnikov z rakom nazofarinksa, ki smo jih obravnavali od maja 2003 do decembra 2006. Bolnikom, vključenim v raziskavo, smo ob ugotovitvi bolezni in ob sledenju po zdravljenju naredili FDG PET/CT preiskavo ter preiskavo s CT ali MRI. Prav tako smo izvide preiskav primerjali z biopsijo tumorja ob ugotovitvi bolezni in s kliničnim stanjem po zdravljenju. Rezultate različnih preiskav smo med seboj statistično primerjali.
Rezultati. Senzitivnost in natančnost PET/CT preiskave in CT/MRI preiskave sta bili enaki ob ugotovitvi bolezni. Ob sledenju bolnikov po zdravljenju je negativni izvid PET/CT preiskave pokazal na popolno remisijo bolezni, senzitivnost in negativna napovedna vrednost sta bili 100%.
Zaključki. 18F FDG PET/CT preiskavo bi lahko uporabljali ob sledenju bolnikov z rakom nazofarnksa. Z njo lahko natančneje ocenjujemo odgovor bolnika na zdravljenje.

Radiol Oncol 2009; 43(4): 258-263.

Retrospektivna raziskava o negativni napovedni vrednosti F-18-FDG koincidentne PET preiskave pri bolnikih s Hodgkinovo boleznijo in ostankom tumorja po zdravljenju

Huić D, Mutvar A, Kinda – Bašić S, Aurer I, Ciglar M, Grošev D, Radman I, Labar B, Dodig D

Izhodišča. Namen raziskave je bil oceniti negativno napovedno vrednost FDG-PET preiskave pri bolnikih s Hodgkinovo boleznijo. FDG-PET preiskavo smo izvajali s koincidentno kamero gama s trojno glavo. Zanimalo nas je, kakšna je vrednost takšne preiskave po zdravljenju prvega reda ali po rešilnem zdravljenju ob ponovitvi bolezni – v primerjavi s podatki zbranimi ob dolgotrajnem sledenju bolnikov.

Metode. Retrospektivno smo analizirali podatke zbrane v Univerzitetni klinični bolnici v Zagrebu v obdobju med junijem 2001 in februarjem 2008. Pregledali smo dokumentacijo 131 zaporedno izbranih bolnikov s Hodgkinovo boleznijo. Pri 73 bolnikih je bila PET preiskava negativna, stari so bili 12-80 let, srednja starost je bila 28 let. Vsi so imeli z biopsijo potrjeno bolezen pred prvim zdravljenjem ali pred rešilnim zdravljenjem, nato pa smo jih sledili vsaj 12 mesecev (od 12 do 69 mesecev, srednja doba opazovanja 23 mesecev). Pri vseh smo naredili ^{18}F-FDG PET preiskavo nekaj mesecev po končanem zdravljenju. Uporabili smo hibridno PET kamero s trojno glavo, s katero smo lahko izvedli koincidenčno slikovno preiskavo. Rezultate preiskav sta interpretirala dva izkušena specialista nuklearne medicine, ki nista poznala izsledke bolnikovih kliničnih in CT preiskav.

Rezultati. Pri 73 od 131 bolnikih je bila PET preiskava negativna in pri 61 od 73 smo preiskavo naredili po kemo/radioterapiji prvega reda. Samo pri 3 od 61 smo ugotovili ponovitev bolezni ob njihovem sledenju (negativna napovedna vrednost 0,95). Pri 12 od 73 bolnikih, ki so imeli rezistentno obliko bolezni, pa smo preiskavo naredili po ponovnem zdravljenju in pri 4 od njih smo ponovitev bolezni ugotovili ob njihovem sledenju (negativna napovedna vrednost 0,66).

Zaključki. PET preiskava s koincidentno kamero gama s trojno glavo ima visoko negativno napovedno vrednost in lahko znatno pomaga pri vodenju bolnika.

Radiol Oncol 2009; 43(4): 267-273.

Povečana citotoksičnost bleomicina in cisplatina po elektroporaciji mišjih celic kolorektalnega karcinoma

Todorović V, Serša G, Flisar K, Čemažar M

Izhodišča. Elektrokemoterapija je lokalna oblika zdravljenja, ki združuje aplikacijo električnih pulzov in kemoterapijo. Kemoterapevtika bleomicin in cisplatin sta učinkovita pri uporabi v elektrokemoterapiji. V kliničnih raziskavah so dokazali učinkovitost elektrokemoterapije pri zdravljenju različnih kožnih in podkožnih tumorjev. Le nekaj raziskav je potekalo na kolorektalnem karcinomu, večinoma z bleomicinom. Namen raziskave je bil določiti občutljivost mišjih celic kolorektalnega karcinoma CMT-93 na elektrokemoterapijo z bleomicinom in cisplatinom za potencialno uporabo v predkliničnih in kliničnih raziskavah kolorektalnega karcinoma.

Metode. Celice CMT-93 smo izpostavili ali samo kemoterapevtiku ali elektrokemoterapiji. S testom klonogenosti smo določili delež preživetja celic po zdravljenju. Prisotnost apoptoze smo merili z aktivnostjo kaspaz-3/7, prisotnost nekroze z morfološko analizo celičnih preparatov in viabilnost celic z MTS testom 16 ur po elektrokemoterapiji.

Rezultati. Po elektrokemoterapiji so bile celice 500-krat bolj občutljive za bleomicin in 2,8-krat bolj občutljive za cisplatin v primerjavi z izpostavljenostjo zgolj kemoterapevtiku. Pri največjih testiranih koncentracijah se je po elektrokemoterapiji značilno zmanjšala viabilnost celic, povečala aktivnost kaspaz-3/7 ter število nekrotičnih celic.

Zaključki. Izpostavitev celic električnim pulzom je povečala citotoksičnost tako bleomicina kot cisplatina. Zmanjšana celična viabilnost je bila zaradi apoptotske in nekrotične oblike celične smrti. Elektrokemoterapija z bleomicinom je bila bolj citotoksična kot elektrokemoterapija s cisplatinom pri izbrani celični liniji kolorektalnega karcinoma.

Radiol Oncol 2009; 43(4): 274-281.

Postoperativna radiokemoterapija pri bolnikih z rakom želodca

Oblak I, Anderluh F, Velenik V

Izhodišča. V raziskavi smo želeli analizirati učinkovitost pooperativne radiokemoterapije s 5-fluorouracilom (5-FU) in levkovorinom (LV) pri bolnikih s karcinomom želodca zdravljenih v eni ustanovi.

Bolniki in metode. Med leti 2001 in 2004 je bilo 123 bolnikov z reseciranim adenokarcinomom želodca zdravljenih s pooperativno sočasno radiokemoterapijo s 5-FU in LV. Pooperativno zdravljenje je bilo sestavljeno iz petih krogov kemoterapije. Bolniki so prejeli intravensko 425 mg/m^2 5-FU in 20 mg/m^2 LV ter bili sočasno obsevani do celokupne doze 45 Gy.

Rezultati. Zdravljenje smo zaključili po protokolu pri 82% bolnikih. Pogostnost in jakost zgodnjih toksičnih sopojavov povzročenih z radiokemoterapijo je bila sprejemljiva. V času analize je bilo živih še 56 bolnikov. Mediani čas sledenja je bil 64,5 meseca (razpon: 51,7-96,4 meseca). Petletno preživetje brez lokoregionalne ponovitve bolezni je bilo 81%, preživetje brez znakov bolezni 48,3%, specifično bolezensko preživetje 50,4% in celokupno preživetje 48,4%. Zajetost kardije želodca z rakom in prejetje nižje doze kemoterapije sta se pokazala kot neodvisna negativna napovedna dejavnika za specifično bolezensko preživetje in celokupno preživetje. Višji T-stadij bolezni in difuzni tip rasti po Laurenu pa sta bila neodvisna negativna napovedna dejavnika le za celokupno preživetje, vendar sta bila tudi za specifično bolezensko preživetje na meji statistične značilnosti.

Zaključki. Pooperativna radiokemoterapija ima pri bolnikih s karcinomom želodca sprejemljive stranske učinke in predvsem zmanjšuje lokoregionalno ponovitev bolezni. Glede na visoko pogostnost oddaljenih zasevkov bo potrebno uvesti bolj učinkovita sistemska zdravljenja.

Radiol Oncol 2009; 43(4): 282-292.

Spremembe krvne slike, indeksa telesne teže, jetrnih encimov in izraženosti indeksa CD64 na levkocitih po kirurškem zdravljenju in obsevanju bolnikov z rakom ustne votline

Dovšak T, Ihan A, Didanovič V, Kansky A, Ihan Hren N

Izhodišča. Namen raziskave je bil oceniti vpliv kirurškega zdravljenja in radioterapije pri zdravljenju napredovalega ploščatoceličnega raka ustne votline. Spremljali smo spremembe naslednjih spremenljivk: indeks telesne teže, krvno sliko, proteine akutne faze, jetrne encime in izraženost CD64 na levkocitih.

Bolniki in metode. 16 bolnikom z napredovalim ploščatoceličnim rakom ustne votline, ki so bili zdravljeni z radikalnimi resekcijami in pooperativnim obsevanjem, smo jemali vzorce periferne venske krvi pred operacijo (T1), po operaciji (T2) ter po obsevanju (T3). V vzorcih smo določali krvno sliko, vrednosti imunoglobulinov G in jetrnih encimov (γ-GT, ALT, AST), kazalce vnetja (C- reaktivni protein, sedimentacijo eritrocitov, albumine, število levkocitov in izraženost CD64 na levkocitih). Za oceno prehranjenosti bolnikov smo ob vsakem odvzemu izračunali indeks telesne teže.

Rezultati. Po kirurškem zdravljenju je bila prisotna anemija, trombocitoza in limfopenija. Prišlo je do povišanja vrednosti proteinov akutne faze, transferaz ter višjega indeksa izraženosti CD64 na monocitih in nevtrofilnih granulocitih. Vrednosti bilirubina, albuminov, proteinov in γ-GT pa so se po operaciji znižale. Vrednosti hemoglobina, levkocitov, C- reaktivnega proteina, sedimentacije eritrocitov, transferaz, bilirubina, albuminov in proteinov so se po obsevanju vrnile na vrednosti pred operacijo, prišlo pa je do znižanja vrednosti limfocitov, γ-GT in indeksa telesne teže. Vrednostih imunoglobulinov G se niso spreminjale ne po operaciji ne po obsevanju. Po obsevanju pa so bile povišane vrednosti indeksa izraženosti CD64 na monocitih in nevtrofilnih granulocitih.

Zaključki. Kirurško zdravljenje je povzročilo precej močnejši vnetni odziv kot zdravljenje z obsevanjem. Limfopenija, ki je bila prisotna že po kirurškem zdravljenju, se je po obsevanju le še stopnjevala.

Radiol Oncol 2009; 43(4): 293-298.

Kakovost življenja pri bolnicah z rakom vratu maternice stadij FIGO IIb po sočasni kemoradioterapiji

Ljuca D, Marosevic G

Izhodišča. Podatki iz literature ne opredelijo natančno kakovosti življenja bolnic po sočasni kemoradioterapiji. Namen naše raziskave je bil ugotoviti kavaliteto življenja takšnih bolnic, ki so bile zdravljenje zaradi raka vratu maternice stadij FIGO IIb, in jo primerjati s kakovostjo življenja pred zdravljenjem.

Metode. 19 bolnicam smo obsevali medenico s tumorsko dozo do 45 Gy v 25 frakcijah in v 5 tednih. Nato smo bolnice dodatno intrakavitarno obsevali z 20-24 Gy v 4-6 frakcijah in pri tem uporabili brahiradioterapijo z visoko hitrostjo doze (HDR). Sočasno so bolnice prejemale kemoterapijo 40 mg/m^2 cisplatina enkrat tedensko. S kemoterapijo smo pričeli zdraviti prvi dan brahiradioterapije in so prejele 4-6 aplikacij. Bolnice so ob ugotovitvi bolezni in 12 mesecev po zdravljenju izpolnile dvoje vprašalnikov o kakovosti življenja. Vprašalnika priporoča Evropska organizacija za raziskavo in zdravljenje raka (EORTC), eden je namenjen bolnikom s kakršnimkoli rakom (EORTC QLQ-C30), drugi pa bolnicam z rakom vratu maternice (EORTC QLQ-Cx24).

Rezultati. Ob primerjavi odgovorov pred in po zdravljenjem smo ugotovili statistično značilno izboljšanje glede kakovosti življenja, zmožnostjo opravljanja vsakdanjih opravil, čustvenega in socialnega stanja, bolečin, utrujenosti in težav v nožnici.

Zaključki. Kakovost življenja bolnic, ki so bile zdravljenje zaradi raka vratu maternice stadij FIGO IIb, je po sočasni kemoradioterapiji znatno boljša.

Notices

*Notices submitted for publication should contain a mailing address, phone and/or fax number and/or e-mail of a **Contact** person or department.*

Lung cancer

January 11-14, 2010
The "AACR-IASLC Joint Conference Molecular Origins of Lung Cancer: Prospects for Personalized Prevention and Therapy" will be held in Coronado, California, USA.
Contact Chairpersons: David P. Carbone, Roy S. Herbst; see: http://www.aacr.org/home/scientists/meetings – workshops/aacr-iaslc-joint-conference-lung-cancer.aspx

Inflammation and immunology

February 1-4, 2010
The 2nd international conference on drug discovery and therapy "Inflammation and Immunology" will be held in Dubai, ZAE.
Contact Organizing Secretariat, ICDDT 2010, Executive Suite Y – 26, PO Box 7917, Saif Zone, Sharjah, UAE; or call: +971-6-5571132; or fax: + 971-6-5571134; or e-mail info@icddt-ii.com; or see http://www.icddt-ii.com

Lung cancer

February 24-28, 2010
The 10th annual meeting "Targeted Therapies of the Treatment of Lung Cancer" will be held in Santa Monica, CA, USA.
E-mail pia.hirsch@ucdenver.edu

Head and neck cancer

February 25-27, 2010
The multidisciplinary symposium on head and neck cancer will be offered in Chandler, Arizona, USA.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502 1550; see http://www/astro.org

Lung cancer

March 5-6, 2010
The 11th European Congress: "Perspectives in Lung Cancer" will be held in Amsterdam, the Netherland.
Contact Customer Service, phone +1 678 242 0906, or e-mail meetings@imedex.com

Oncology

March 10-14, 2010
The NCCN 15th Annual Conference "Clinical Practice Guidelines & Quality Cancer Care" will be held in Hollywood, Florida, USA.
Contact National Comprehensive Cancer Network, 275 Commerce Drive, Suite 300, Fort Washington, PA 19034, USA; or phone +1 215 690 0300; or fax +1 215 690 0280; or e-mail support@nccn.ecimail.net

Lung cancer

April 28 - May 1, 2010
The 2nd European IASLC/ESMO Lung Cancer Conference will be held in Geneva, Switzerland.
See http://www.iaslc.org

Clinical oncology

June 4-8, 2010
The American Society of Clinical Oncology Conference (ASCO 2010) will be offered in Chicago, USA.
E-mail enews@asco.org; or see http://www/asco.org

Lung cancer

July 29-31, 2010
The IASLC Latin American Meeting will be held in Buenos Aires, Argentina.
See http://www.iaslc.org

Mesothelioma

August 31 – September 3, 2010
The 10th International Conference of the International Mesothelioma Interest Group will be held in Kyoto, Japan.
Contact Secretariat, IMIG 2010, c/o Congress Corporation, 3-6-13 Awajimachi, Chuo-ku, Osaka,Japan; or phone +81-6-6229-2555; or fax +81-6-6229-2556; or e-mail imig2010@congre.co.jp

Thoracic oncology

October 7-9, 2010
The 2nd International Thoracic Congress Dresden will be held in Dresden, Germany.
E-mail profmanegold@t-online.de

Oncology

October 8-12, 2010
The "35th ESMO Congress" will take place in Milan, Italy.
Contact ESMO Head Office, Congress Department, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland; or call +41 (0)91 973 19 19; or fax +41 (0)91 973 19 18; or e-mail congress@esmo.org; or see http://www.esmo.org

Nuclear medicine

October 9-13, 2010
The "EANM'10 Annual Congress of the European Association of Nuclear Medicine" will take place in Vienna, Austria.
Contact EANM Executive Secretariat and call +43 1 212 80 30; or fax +43 1 212 80 309; or e-mail office@ eanm.org; or see http://www. eanm.org

Therapeutic radiology and oncology

October 31 – November 4, 2010
The "American Society for Therapeutic Radiology and Oncology Annual Meeting ASTRO" will take place in San Diego, California, USA.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; or see http://www.astro.org

Radiation oncology

November 13-19, 2010
The ESO/ESTRO masterclass in radiation oncology will be offered in Cascais, Portugal.
Contact Chiara Gasparotto, European School of Radiotherapy, ESTRO Office, Av. E. Mounier 83, 1200 Brussels, Belgium; or phone +32 2 775 9337; or fax +32 2 779 5494; or e-mail cgasparotto@estro.org; or see www.eso. Net or www.estro.org

Lung cancer

December 2-4, 2010
The 4th Asia Pacific Lung Cancer Conference (APLCC 2010) will be held in Seoul, South Korea.
E-mail hjk3425@skku.edu

Lung cancer

December 3-5, 2010
The 12th Central European Lung Cancer Conference (CELCC) will be held in Budapest, Hungary.
E-mail ostorosgyula@freemail.hu

Thoracic oncology

December 9-11, 2010
The ASCO/ASTRO/IASLC/University of Chicago Multidisciplinary Symposium in Thoracic Oncology will be held in Chicago, IL, USA.
E-mail evokes@medicine.bsd.uchicago.edu

Clinical oncology

June 3-7, 2011
The American Society of Clinical Oncology Conference (ASCO 2010) will be offered in Chicago, USA.
E mail enews@asco.org; or see http://www/asco.org

Lung cancer

July 3-7, 2011
The "14th World Conference on Lung Cancer" will be offered in Amsterdam, The Netherlands.
See http://www.iaslc.org

Oncology

September 23-27, 2011
The "16th ECCO and 36th ESMO Multidisciplinary Congress" will be offered in Stockholm, Sweden.
See http://www.ecco-org.eu

Nuclear medicine

October 15-19, 2011
The "EANM'11 Annual Congress of the European Association of Nuclear Medicine" will take place in Birmingham, United Kingdom.
Contact EANM Executive Secretariat and call +43 1 212 80 30; or fax +43 1 212 80 309; or e-mail office@ eanm.org; or see http://www. eanm.org

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Oncology

September 27 – October 1, 2013
The "17th ECCO and 38th ESMO Multidisciplinary Congress" will be offered in Amsterdam, The Netherlands.
See http://www.ecco-org.eu

Lung cancer

2013
The "15th World Conference on Lung Cancer" will be offered in Sydney, Australia.
See http://www.iaslc.org

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.

Authors Index 2009

Subject Index 2009

Fundacija "Docent dr. J. Cholewa"
je neprofitno, neinstitucionalno in nestrankarsko
združenje posameznikov, ustanov in organizacij, ki želijo
materialno spodbujati in poglabljati raziskovalno
dejavnost v onkologiji.

Dunajska 106
1000 Ljubljana

ŽR: 02033-0017879431

Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the final quarter of 2009

One of the main activities of Dr. J. Cholewa Foundation for Cancer Reasearch and Education is to support oncology related scientific research and cancer education in Slovenia. The Foundation carefully assesses the requests for research grants and scholarships submitted by experts in oncology and other scientific activities in Slovenia, concerned with oncology, as in its opinion the advances in cancer research, therapy and education must not be hindered for the simple lack of financial support. The Foundation strongly supports the implementation of all recent advances in cancer therapy and cancer education into everyday clinical and health promotion practice. Hopefully, the results of cancer research, supported by the Foundation, will find their way into the practical application in hospitals accross Slovenia as rapidly as possible.

The Foundation considers the spread of advanced knowledge in cancer research, cancer therapy and cancer education as of its main activities. The Foundation therefore continues to support the regular publication of "Radiology and Oncology" international medical scientific journal, that is edited, published and printed in Ljubljana, Slovenia. "Radiology and Oncology" is an open access journal, available free of charge on its own website, thus allowing its users and readers to access it free of charge. This activity is in a special way complementing the more direct approaches mentioned above and represents an important additional benefit for the ever increasing number of patients with various types of cancer in Slovenia, since the incidence rates of many cancer have kept rising in the recent years in this country. The Foundation is therefore active in promoting cancer research, cancer therapy and education to increase their impact in general population and among scientists with a budding interest in this field of experimental and clinical medicine.

In conclusion, the ultimate and most important goal of the majority of Foudation's activities is to convey the latest cancer diagnostic, therapy and education methods and knowledge to everyday research, clinical and public environment in Slovenia.

Andrej Plesničar, MD, MSc
Tomaž Benulič, MD
Borut Štabuc, MD, PhD

LABORMED

ZASTOPA PODJETJA:

MENTOR

Prsni vsadki napolnjeni s silikonskim gelom, ekspanderji in drugi pripomočki pri rekonstrukciji dojk

Köttermann (Nemčija):
laboratorijsko pohištvo, varnostne omare za kisline, luge, topila, pline in strupe, ventilacijska tehnika in digestorji

Ehret (Nemčija):
Laminar flow tehnika, inkubatorji, sušilniki, suhi sterilizatorji in oprema za laboratorijsko vzrejo živali - kletke

Angelantoni scientifica (Italija):
hladilna tehnika in aparati za laboratorije, transfuzijo, patologijo in sodno medicino

Dako (Danska):
testi za aplikacijo v imunohistokemiji, patologiji, mikrobiologiji, virologiji, mono- in poliklonalna protitelesa

Corning (Amerika):
specialna laboratorijska plastika za aplikacijo v imunologiji, mikrobiologiji, virologiji, ipd., mehanske eno- in večkanalne pipete in nastavki

Sakura finetek (Evropa):
aparati za pripravo histoloških preparatov: mikro-inkriotomi, zalivalci, tkivni procesorji, barvalci, pokrivalci

Micronic (Nizozemska):
sistemi za shranjevanje vzorcev, pipete, nastavki za pipete

Integra Biosciens (Švica):
laboratorijska oprema za mikrobiologijo, biologijo celic, molekularno biologijo in biotehnologijo

Implantech (Amerika):
obrazni in glutealni vsadki

SpectrumDesigns MEDICAL (Amerika):
moški pektoralni vsadki

Biomerica (Amerika):
hitri testi za diagnostiko, EIA /RIA testi

Byron (Amerika):
liposuktorji in kanile za liposukcijo

LABORMED d.o.o.
Bežigrajski dvor
Peričeva 29, Ljubljana
Tel.: (0)1 436 49 01
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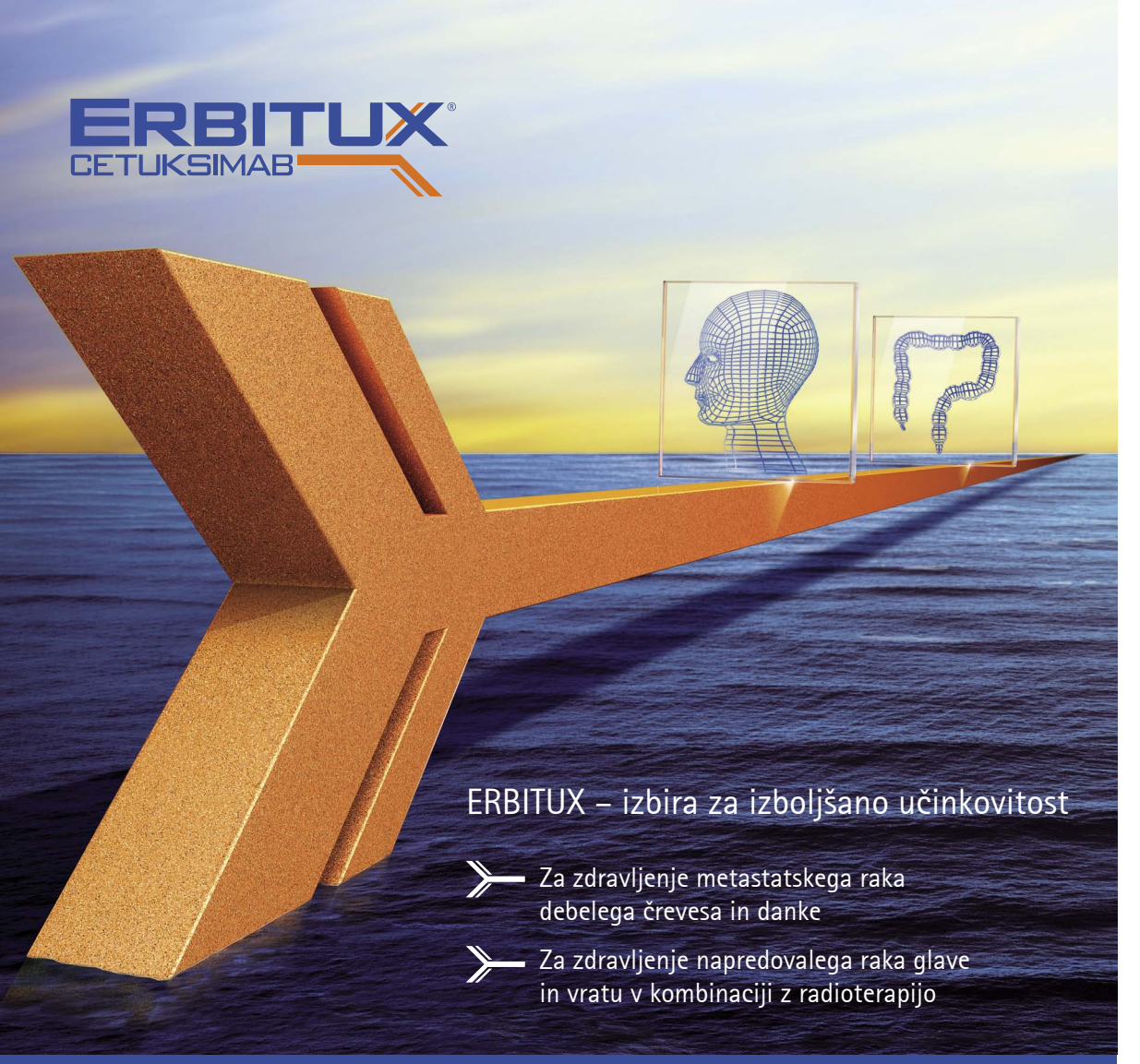

Merck Serono Onkologija / biološko zdravljenje za boljšo kakovost življenja

Erbitux 5 mg/ml raztopina za infundiranje (skrajšana navodila za uporabo)

Cetuksimab je monoklonsko IgG_1 protitelo, usmerjeno proti receptorju za epidermalni rastni faktor (EGFR). **Terapevtske indikacije:** Zdravilo Erbitux je indicirano za zdravljenje bolnikov z metastatskim kolorektalnim rakom in nemutiranim tipom KRAS; v kombinaciji s kemoterapijo in kot samostojno zdravilo pri bolnikih, pri katerih zdravljenje z oksaliplatinom in irinotekanom ni bilo uspešno. Zdravilo Erbitux je v kombinaciji z radioterapijo indicirano za zdravljenje bolnikov z lokalno napredovalim rakom skvamoznih celic glave in vratu. **Odmerjanje in način uporabe:** Zdravilo Erbitux pri vseh indikacijah infundirajte enkrat na teden. Začetni odmerek je 400 mg cetuksimaba na m^2 telesne površine. Vsi naslednji tedenski odmerki so vsak po 250 mg/m^2. **Kontraindikacije:** Zdravilo Erbitux je kontraindicirano pri bolnikih z znano hudo preobčutljivostno reakcijo (3. ali 4. stopnje) na cetuksimab. **Posebna opozorila in previdnostni ukrepi:** Če pri bolniku nastopi blaga ali zmerna reakcija, povezana z infundiranjem, lahko zmanjšate hitrost infundiranja. Priporočljivo je, da ostane hitrost infundiranja na nižji vrednosti tudi pri vseh naslednjih infuzijah. Če se pri bolniku pojavi huda kožna reakcija (≥ 3. stopnje po kriterijih *US National Cancer Institute, Common Toxicity Criteria;* NCI-CTC), morate prekiniti terapijo s cetuksimabom. Z zdravljenjem smete nadaljevati le, če se je reakcija pomirila do 2. stopnje. Priporoča se določanje koncentracije elektrolitov v serumu pred zdravljenjem in periodično med zdravljenjem s cetuksimabom. Po potrebi se priporoča nadomeščanje elektrolitov. Posebna previdnost je potrebna pri oslabljenih bolnikih in pri tistih z obstoječo srčno-pljučno boleznijo. Neželeni učinki: Zelo pogosti (≥ 1/10): dispneja, blago do zmerno povečanje jetrnih encimov, kožne reakcije, blage ali zmerne reakcije povezane z infundiranjem, blag do zmeren mukozitis. Pogosti (≥ 1/100, < 1/10): konjunktivitis, hude reakcije povezane z infundiranjem. Pogostost ni znana: Opazili so progresivno zniževanje nivoja magnezija v serumu, ki pri nekaterih bolnikih povzroča hudo hipomagneziemijo. Glede na resnost so opazili tudi druge elektrolitske motnje, večinoma hipokalciemijo ali hipokaliemijo. **Posebna navodila za shranjevanje:** Shranjujte v hladilniku (2 °C - 8 °C). Ne zamrzujte**. Vrsta ovojnine in vsebina:** 1 viala po 20 ml ali 100 ml. Imetnik dovoljenja za promet: Merck KGaA, 64271 Darmstadt, Nemčija. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila (EMEA) http://www.emea.europa.eu.

Dodatne informacije so vam na voljo pri: Merck d.o.o., Dunajska cesta 119, 1000 Ljubljana, tel.: 01 560 3810, faks: 01 560 3831, el. pošta: info@merck.si

www.oncology.merck.de

MERCK SERONO

Arimidex®
anastrozol

Posodobili smo slovar

Skrajšan povzetek glavnih značilnosti zdravila Arimidex® 1 mg filmsko obložene tablete

Sestava zdravila: Ena tableta vsebuje 1 mg anastrozola.
Indikacije: Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji. Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom. Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.
Odmerjanje in način uporabe: Odrasle (tudi starejše) bolnice: 1 tableta po 1 mg peroralno, enkrat na dan. Odmerka zdravila ni treba prilagajati pri bolnicah z blago ali zmerno ledvično odpovedjo ali blagim jetrnim odpovedovanjem. Pri zgodnjem raku je priporočljivo trajanje zdravljenja 5 let.
Glavni neželeni učinki: Zelo pogosti (≥ 10 %): navali vročine, običajno blagi do zmerni. Pogosti (≥ 1 % in < 10 %): astenija, bolečine/okorelost v sklepih, suhost vagine, razredčenje las, izpuščaji, slabost, diareja, glavobol (vsi običajno blagi do zmerni)
Posebna opozorila in previdnostni ukrepi: Uporabe Arimidexa ne priporočamo pri otrocih, ker njegova varnost in učinkovitost pri njih še nista raziskani. Menopavzo je potrebno biokemično določiti pri vseh bolnicah, kjer obstaja dvom o hormonskem statusu. Ni podatkov o varni uporabi Arimidexa pri bolnicah z zmerno ali hudo jetrno okvaro ali hujšo ledvično odpovedjo (očistek kreatinina manj kakor 20 ml/min (oziroma 0,33 ml/s)). Pri ženskah z osteoporozo ali pri ženskah s povečanim tveganjem za razvoj osteoporoze je treba določiti njihovo mineralno gostoto kosti z denzitometrijo, na primer s slikanjem DEXA na začetku zdravljenja, pozneje pa v rednih intervalih. Po potrebi je treba začeti z zdravljenjem ali preprečevanjem osteoporoze in to skrbno nadzorovati. Ni podatkov o uporabi anastrozola z analogi LHRH. Arimidex znižuje nivo estrogena v obtoku, zato lahko povzroči zmanjšanje mineralne kostne gostote. Trenutno ni na voljo ustreznih podatkov o učinku bifosfonatov na izgubo mineralne kostne gostote, povzročene z anastrozolom, ali njihovi koristi, če se uporabijo preventivno. Zdravilo vsebuje laktozo.
Kontraindikacije: Arimidex je kontraindiciran pri: ženskah pred menopavzo, nosečnicah in doječih materah, bolnicah s hujšo ledvično odpovedjo (očistek kreatinina manj kot 20 ml/min (oziroma 0,33 ml/s)), bolnicah z zmernim do hudim jetrnim obolenjem, bolnicah, ki imajo znano preobčutljivost za anastrozol ali za katerokoli pomožno snov. Zdravila, ki vsebujejo estrogen, ne smete dajati sočasno z Arimidexom, ker bi se njegovo farmakološko delovanje izničilo. Sočasno zdravljenje s tamoksifenom.
Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Klinične raziskave o interakcijah z antipirinom in cimetidinom kažejo, da pri sočasni uporabi Arimidexa in drugih zdravil klinično pomembne interakcije, posredovane s citokromom P450, niso verjetne. Pregled baze podatkov o varnosti v kliničnih preskušanjih pri bolnicah, ki so se zdravile z Arimidexom in sočasno jemale druga pogosto predpisana zdravila, ni pokazal klinično pomembnih interakcij.
Imetnik dovoljenja za promet: AstraZeneca UK Limited, 15 Stanhope Gate, London, W1K 1LN, Velika Britanija
Režim predpisovanja zdravila: Rp/Spec
Datum priprave informacije: april 2007

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.

Dodatne informacije in literatura so na voljo pri:
AstraZeneca UK Limited
Podružnica v Sloveniji
Verovškova ulica 55
1000 Ljubljana

in na spletnih straneh:
www.arimidex.net
www.bco.org
www.breastcancersource.com

AstraZeneca
ONKOLOGIJA

ARI 03/07 P

*adjuvant [ae´džuv*nt]*

1. *adjective* pomagljiv, koristen; *~ treatment with Arimidex:* Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji.

*advanced [*dva:nst]*

1. *adjective* napreden; zvišan (cene); to be ~ napredovati; ~ in years visoke starosti; *treatment of ~ breast cancer with Arimidex:* Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.

switch [swič]

1. *transitive verb* udariti, bičati s šibo (z repom); šibati z, hitro mahati z; naglo pograbiti; railway ranžirati, zapeljati (usmeriti) (vlak) na drug tir; electrical vključiti, vklopiti; spremeniti (pogovor), obrniti drugam (tok misli); to ~ back to figuratively (v mislih) vrniti se na;
~ to Arimidex: Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom.

odprto

Novartis Oncology prinaša širok spekter inovativnih zdravil, s katerimi poskuša spremeniti življenje bolnikov z rakavimi in hematološkimi obolenji.

Ta vključuje zdravila kot so Glivec® (imatinib), Tasigna® (nilotinib), Exjade® (deferasiroks), Zometa® (zoledronska kislina), Sandostatin® LAR® (oktreotid/i.m. injekcije) in Femara® (letrozol).

Novartis Oncology ima tudi obširen razvojni program, ki izkorišča najnovejša spoznanja molekularne genomike, razumskega načrtovanja in tehnologij za odkrivanje novih učinkovin.

glivec® imatinib

Tasigna® (nilotinib)

EXJADE® deferasiroks

ZOMETA® zoledronska kislina

Sandostatin® LAR® oktreotid/i.m. injekcije

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Samo za strokovno javnost.

NVS-JA-01/09-SI

Ime vse pove

Gemcitabin Lek

gemcitabin

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Gemcitabin Lek 200 mg in 1 g prašek za raztopino za infundiranje
Sestava: Vsaka viala vsebuje 200 mg ali 1000 mg gemcitabina (v obliki gemcitabinijevega klorida). Vsak ml zdravila vsebuje 40 mg gemcitabina po redčenju na 5 ml (Gemcitabine Lek 200 mg) ali 40 mg gemcitabina po redčenju na 25 ml (Gemcitabiln Lek 1 g). **Indikacije:** Zdravilo prve izbire za zdravljenje bolnikov z lokalno napredovalim ali metastazirajočim nedrobnoceličnim pljučnim rakom. Za zdravljenje lokalno napredovalega ali metastazirajočega adenokarcinoma trebušne slinavke. Za zdravljenje lokalno napredovalega ali metastazirajočega raka na mehurju v kombinaciji z drugimi citostatičnimi zdravili. V kombinaciji s paklitakselom za zdravljenje bolnikov z neoperabilnim, lokalno ponavljajočim se ali metastazirajočim rakom na dojki, pri katerih se je bolezen ponovno pojavila po adjuvantni/neoadjuvantni kemoterapiji, ki je morala vključevati antraciklin, razen če ni bil klinično kontraindiciran.
Odmerjanje in način uporabe: Zdravljenje mora začeti zdravnik, ki ima precej izkušenj z zdravljenjem s citotoksičnimi zdravili. *Nedrobnocelični pljučni rak pri odraslih: Kombinirana uporaba*: Pri tritedenskem načrtu gemcitabin v odmerku 1250 mg/m² v 30-minutni intravenski infuziji prvi in osmi dan vsakega 21-dnevnega ciklusa. Pri štiritedenskem načrtu gemcitabin v odmerku 1000 mg/m² v 30-minutni intravenski infuziji prvi, osmi in petnajsti dan vsakega 28-dnevnega ciklusa. Cisplatin v odmerkih med 75 in 100 mg/m², enkrat na vsake tri ali štiri tedne. *Uporaba enega samega zdravila:* Priporočeni odmerek gemcitabina znaša 1000 mg/m² v 30-minutni intravenski infuziji, ponavljajoče enkrat tedensko v obdobju treh tednov, čemur sledi en teden premora. Štiritedenski ciklus se nato ponovi. *Rak trebušne slinavke:* Priporočeni odmerek znaša 1000 mg/m² v 30-minutni intravenski infuziji, ponavljajoče enkrat tedensko v obdobju do sedem tednov, čemur sledi en teden premora. Naslednji ciklusi morajo biti sestavljeni iz injiciranj enkrat tedensko v obdobju treh zaporednih tednov izmed vsakih štirih tednov. *Rak na mehurju:* Priporočeni odmerek znaša 1000 mg/m² v 30-minutni infuziji. Odmerek je treba dati prvi, osmi in petnajsti dan vsakega 28-dnevnega ciklusa v kombinaciji s cisplatinom. Cisplatin se daje v priporočenem odmerku 70 mg/m² prvi dan po dajanju gemcitabina oziroma drugi dan vsakega 28-dnevnega ciklusa. Ta štiritedenski ciklus se zatem ponovi. *Rak na dojki:* Priporočljiva je uporaba gemcitabina v kombinaciji s paklitakselom, pri čemer se paklitaksel (v odmerku 175 mg/m²) uporabi prvi dan v tri ure trajajoči intravenski infuziji, čemur sledi gemcitabin (v odmerku 1250 mg/m²) v 30 do 60 minut trajajoči intravenski infuziji prvi in osmi dan vsakega 21-dnevnega ciklusa. Pred začetkom dajanja kombinacije gemcitabin + paklitaksel mora pri bolnikih absolutno število granulocitov znašati najmanj 1,5 (× 10⁹/l). *Preverjanja:* Pri bolnikih, ki prejemajo gemcitabin, je treba pred dajanjem vsakega odmerka preverjati število trombocitov, levkocitov in granulocitov. Če je potrebno, se odmerek gemcitabina ob prisotnosti hematološke toksičnosti lahko zmanjša ali se ga preneha uporabljati. Treba je izvajati redne klinične preglede in preverjati delovanje jeter in ledvic, da bi lahko zaznali nehematološke škodljive vplive.
Kontraindikacije: Preobčutljivost za gemcitabin ali katerokoli pomožno snov. Uporaba med dojenjem pri ženskah, ki otroke dojijo. Sočasna uporaba s cepivom proti rumeni mrzlici. Kombinacija gemcitabina s cisplatinom pri bolnikih s hudo ledvično okvaro.

Posebna opozorila in previdnostni ukrepi: Gemcitabin lahko kratkotrajno zavre delovanje kostnega mozga, kar se kaže v levkopeniji, trombocitopeniji in anemiji.
Gemcitabin je treba uporabljati previdno pri bolnikih z okvarjeno ledvično funkcijo. Z uporabo gemcitabina je treba prenehati ob prvem pojavu kakršnihkoli znakov mikroangiopatske hemolitične anemije, kot je na primer hitro padajoča raven hemoglobina s spremljajočo trombocitopenijo, povečanje koncentracije bilirubina in kreatinina v serumu, povečanje ravni sečninskega dušika v krvi ali LDL, kar lahko nakazuje razvoj hemolitičnega uremičnega sindroma. Odpoved ledvic je lahko tudi po prenehanju zdravljenja ireverzibilna in lahko je potrebna dializa. Ne glede na to, ali zdravilo uporablja moški ali ženska, je treba med zdravljenjem upoštevati ukrepe za preprečevanje nosečnosti.
Medsebojno delovanje z zdravili in druge oblike interakcij: Sočasno zdravljenje z obsevanjem (ki se izvaja obenem ali s časovnim presledkom ≤ 7 dni). Zaporedno zdravljenje z obsevanjem (ki se izvaja s časovnim presledkom > 7 dni). Gemcitabin deluje radiosenzitizirajoče. Zaradi povečanega tveganja za trombozo pri bolnikih z rakom je uporaba antikoagulacijskega zdravljenja pogosta. Velika razlika v koagulacijskem statusu med posamezniki v času bolezni in možnost medsebojnega delovanja oralnih antikoagulantov in kemoterapije zahteva bolj pogosto spremljanje INR-ja v primeru uporabe antikoagulantov. *Kontraindicirana sočasna uporaba*: cepivo proti rumeni mrzlici. *Nepriporočljiva sočasna uporaba*: živa, oslabljena cepiva (razen rumene mrzlice). *Sočasna uporaba, ki zahteva premislek:* ciklosporin, takrolimus.
Vpliv na sposobnost vožnje in upravljanja s stroji: Gemcitabin lahko povzroči blago do zmerno zaspanost. Bolnike je zato treba posvariti pred vožnjo ali upravljanjem s stroji, dokler se ne izkaže, da zdravilo nanje nima omenjenega vpliva.
Neželeni učinki: Na pogostnost in hudost neželenih učinkov vplivajo odmerek, hitrost infundiranja in časovni presledki med odmerki. *Zelo pogosti* (> 1/10): anemija, levkopenija, trombocitopenija, nevtropenija, dispneja, navzea, bruhanje, povečane vrednosti jetrnih transaminaz (AST in ALT) in alkalne fosfataze, alergijski kožni izpuščaj, ki ga pogosto spremlja srbenje; plešavost – običajno blaga, hematurija, proteinurija, edemi/periferni edemi, gripi podobni simptomi (povečana telesna temperatura, glavobol, bolečine v hrbtu, drgetanje, bolečine v mišicah, astenija, pomanjkanje teka, kašelj, rinitis, občutek slabosti, znojenje, motnje spanja). *Pogosti* (> 1/100 do < 1/10): febrilna nevtropenija, zaspanost, stomatitis in razjede v ustih, driska, zaprtje, povečana koncentracija bilirubina, povečana telesna temperatura, astenija. Neželeni učinki, zaradi katerih je treba odmerek omejiti, so zmanjšanja števila trombocitov, levkocitov in granulocitov.
Oprema: Škatla z eno vialo s praškom.
Način izdaje zdravila: H
Imetnik dovoljenja za promet: Lek farmacevtska družba d.d., Verovškova 57, 1526 Ljubljana, Slovenija.
Informacija pripravljena: julij 2008

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Temodal 20 mg, 100 mg, 140mg, 180 mg, 250 mg.

Sestava zdravila: Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg, 140 mg, 180 mg ali 250 mg temozolomida.

Terapevtske indikacije Temodal kapsule so indicirane za zdravljenje bolnikov z:

- za zdravljenje novo diagnosticiranega glioblastoma multiforme, sočasno z radioterapijo in kasneje kot monoterapija
- malignim gliomom, na primer multiformnim glioblastomom ali anaplastičnim astrocitomom, ki se po standardnem zdravljenju ponovi ali napreduje.

Odmerjanje in način uporabe Temodal smejo predpisati le zdravniki, ki imajo izkušnje z zdravljenjem možganskih tumorjev. **Odrasli bolniki z novo diagnosticiranim glioblastomom multiforme** Temodal se uporablja v kombinaciji z žariščno radioterapijo (faza sočasne terapije), temu pa sledi do 6 ciklov monoterapije z temozolomidom. **Faza sočasne terapije** Zdravilo Temodal naj bolnik jemlje peroralno v odmerku 75 mg/m^2 na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Odmerka ne boste zmanjševali, vendar se boste vsak teden odločili o morebitni odložitvi jemanja temozolomida ali njegovi ukinitvi na podlagi kriterijev hematološke in nehematološke toksičnosti. Zdravilo Temodal lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije do 49 dni, če so izpolnjeni vsi od naslednjih pogojev: absolutno število nevtrofilcev ≥ 1,5 x 109/l, število trombocitov ≥ 100 x 109/l, skupni kriteriji toksičnosti (SKT) za nehematološko toksičnost ≤ 1. stopnje (z izjemo alopecije, slabosti in bruhanja). Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko. **Faza monoterapije** Štiri tedne po zaključku faze sočasnega zdravljenja z zdravilom Temodal in radioterapijo naj bolnik jemlje zdravilo Temodal do 6 ciklov monoterapije. V 1. ciklu (monoterapija) je odmerek zdravila 150 mg/m^2 enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m^2, če je SKT za nehematološko toksičnost za 1. cikel stopnje ≤ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (AŠN) ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Če odmerka niste povečali v 2. ciklusu, ga v naslednjih ciklusih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m^2 na dan v prvih 5 dneh vsakega naslednjega ciklusa, razen če nastopi toksičnost. Med zdravljenjem morate pregledati celotno krvno sliko na 22. dan (21 dni po prvem odmerku zdravila Temodal). **Ponavljajoči se ali napredujoči maligni gliom Odrasli bolniki** Posamezen ciklus zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo Temodal peroralno v odmerku 200 mg/m^2 enkrat na dan prvih 5 dni, temu pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so že bili zdravljeni s kemoterapijo, je začetni odmerek 150 mg/m^2 enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m^2 enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov (glejte poglavje 4.4). **Pediatrični bolniki** Pri bolnikih starih 3 leta ali starejših, posamezen ciklus zdravljenja traja 28 dni. Temodal naj jemljejo peroralno v odmerku 200 mg/m^2 enkrat na dan prvih 5 dni, potem pa naj sledi 23-dnevni premor (skupaj 28 dni). Otroci, ki so že bili zdravljeni s kemoterapijo, naj prejmejo začetni odmerek 150 mg/m^2 enkrat na dan 5 dni, s povečanjem na 200 mg/m^2 enkrat na dan 5 dni v naslednjem ciklusu, če ni bilo hematoloških toksičnih učinkov (glejte poglavje 4.4). **Bolniki z motnjami v delovanju jeter ali ledvic** Pri bolnikih z blagimi ali zmernimi motnjami v delovanju jeter je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Podatki o uporabi zdravila Temodal pri bolnikih s hudimi motnjami v delovanju jeter (razred III po Child-u) ali motnjami v delovanju ledvic niso na voljo. Na podlagi farmakokinetičnih lastnosti temozolomida obstaja majhna verjetnost, da bo pri bolnikih s hudimi motnjami v delovanju jeter ali ledvic potrebno zmanjšanje odmerka zdravila. Kljub temu je potrebna previdnost pri uporabi zdravila Temodal pri teh bolnikih. **Starejši bolniki:** Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub temu je potrebna posebna previdnost pri uporabi zdravila Temodal pri starejših bolnikih. **Način uporabe** Temodal mora bolnik jemati na tešče. Temodal kapsule mora bolnik pogoltniti cele s kozarcem vode in jih ne sme odpirati ali žvečiti. Predpisani odmerek mora vzeti v obliki najmanjšega možnega števila kapsul. Pred jemanjem zdravila Temodal ali po njem lahko bolnik vzame antiemetik Če po zaužitju odmerka bruha, ne sme še isti dan vzeti drugega odmerka. **Kontraindikacije** Temodal je kontraindiciran pri bolnikih, ki imajo v anamnezi preobčutljivostne reakcije na sestavine zdravila ali na dakarbazin (DTIC). Temodal je kontraindiciran tudi pri bolnikih s hudo mielosupresijo. Temodal je kontraindiciran pri ženskah, ki so noseče ali dojijo. **Posebna opozorila in previdnostni ukrepi** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da imajo bolniki, ki so sočasno prejemali zdravilo Temodal in radioterapijo, še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s Pneumocystis carinii (PCP). Profilaksa proti tovrstni pljučnici je torej potrebna pri vseh bolnikih, ki sočasno prejemajo zdravilo Temodal in radioterapijo v okviru 42-dnevne sheme zdravljenja (do največ 49 dni), ne glede na število limfocitov. Če nastopi limfopenija, mora bolnik nadaljevati s profilakso, dokler se limfopenija ne povrne na stopnjo ≤ 1. Antiemetična terapija: Z jemanjem zdravila Temodal sta zelo pogosto povezana slabost in bruhanje. **Laboratorijske vrednosti**: Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC mora biti ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Na 22. dan (21 dni po prvem odmerku) ali v roku 48 ur od navedenega dne, morate pregledati celotno krvno sliko in jo nato spremljati vsak teden, dokler ni ANC nad 1,5 x 109/l in število trombocitov nad 100 x 109/l. Če med katerimkoli ciklusom ANC pade na < 1,0 x 109/l ali število trombocitov na < 50 x 109/l, morate odmerek zdravila v naslednjem ciklusu zmanjšati za eno odmerno stopnjo. Odmerne stopnje so 100 mg/m^2, 150 mg/m^2 in 200 mg/m^2. Najmanjši priporočeni odmerek je 100 mg/m^2. **Moški bolniki** Temozolomid lahko deluje genotoksično, zato morate moškim, ki se zdravijo z temozolomidom svetovati, da naj ne zaplodijo otroka še šest mesecev po zdravljenju. **Interakcije** Sočasna uporaba zdravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali monometiltriazenoimidazol karboksamida (MTIC). Jemanje zdravila Temodal s hrano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje površino pod krivuljo (AUC). Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko klinično pomembna, naj bolniki jemljejo zdravilo Temodal brez hrane. Analiza populacijske farmakokinetike v preskušanjih druge faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi mielosupresivnimi učinkovinami la hko poveča verjetnost mielosupresije. **Nosečnost** Študij na nosečih ženskah ni bilo. Predklinične študije na podganah in kuncih z odmerkom 150 mg/m^2 so pokazale teratogenost in/ali toksičnost za plod. Zato naj noseče ženske načeloma ne bi jemale zdravila Temodal. Če pa je uporaba v času nosečnosti nujna, morate bolnico opozoriti na možne nevarnosti zdravila za plod. Ženskam v rodni dobi svetujte, naj med zdravljenjem z zdravilom Temodal preprečijo zanositev. **Dojenje** Ni znano, ali se temozolomid izloča v materino mleko, zato ženske, ki dojijo ne smejo jemati zdravila Temodal. **Neželeni učinki** V kliničnih preskušanjih so bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %). Oba učinka sta bila ponavadi 1. ali 2. stopnje (od 0 do 5 epizod bruhanja v 24 urah) in sta prenehala sama, ali pa ju je bilo mogoče hitro obvladati s standardnim antiemetičnim zdravljenjem. Incidenca hude slabosti in bruhanja je bila 4 %. Laboratorijski izvidi: Trombocitopenija in. nevtropenija 3. in. 4. stopnje sta se pojavili pri 19 % in. 17 % bolnikov, zdravljenih zaradi malignega glioma. Zaradi njiju je bila potrebna hospitalizacija in/ali prekinitev zdravljenja z zdravilom Temodal pri 8 % in. 4 % bolnikov. Mielosupresija je bila predvidljiva (ponavadi se je pojavila v prvih nekaj ciklusih in je bila najizrazitejša med 21. in 28. dnem), okrevanje pa je bilo hitro, ponavadi v 1 do 2 tednih. Opazili niso nobenih dokazov kumulativne mielosupresije. Trombocitopenija lahko poveča tveganje za pojav krvavitev, nevtropenija ali levkopenija pa tveganje za okužbe. **Imetnik dovoljenja za promet** SP Europe 73, rue de Stalle B-1180 Bruxelles Belgija. **Način in režim izdaje** Zdravilo se izdaja samo na recept, uporablja pa se pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Datum priprave informacije** marec 2009.

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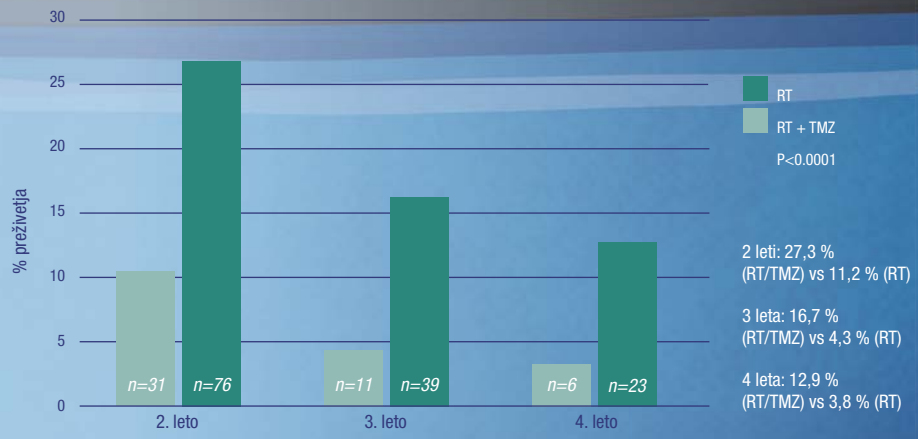
Resnični napredek

Pomembno izboljšanje preživetja potrjeno tudi ob daljšem spremljanju bolnikov

Izboljšanje celokupnega preživetja pri bolnikih z novo odkritim glioblastomom multiforme

Celokupno preživetje



2 leti: 27,3 %
(RT/TMZ) vs 11,2 % (RT)

3 leta: 16,7 %
(RT/TMZ) vs 4,3 % (RT)

4 leta: 12,9 %
(RT/TMZ) vs 3,8 % (RT)

Literatura: 1 Stupp R, Mason WP, van den Bent MJ, s sod. RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GLIOBLASTOMA N Engl J Med.2005;352:987-996. 2 Mirmanoff RO et al; IS LONG-TERM SURVIVAL IN GLIOBLASTOMA POSSIBLE?; 49th annual meeting of the ASRO, Los Angeles, okt. 2007.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Samo za strokovno javnost.

Ime zdravila: Tarceva 25 mg/100 mg/150 mg filmsko obložene tablete
Kakovostna in količinska sestava: Ena filmsko obložena tableta vsebuje 25 mg, 100 mg ali 150 mg erlotiniba (v obliki erlotinibijevega klorida).
Terapevtske indikacije: Nedrobnocelični rak pljuč: Zdravilo Tarceva je indicirano za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč po neuspehu vsaj ene predhodne kemoterapije. Pri predpisovanju zdravila Tarceva je treba upoštevati dejavnike, povezane s podaljšanim preživetjem. Koristnega vpliva na podaljšanje preživetja ali drugih klinično pomembnih učinkov zdravljenja niso dokazali pri bolnikih z EGFR-negativnimi tumorji. Rak trebušne slinavke: Zdravilo Tarceva je v kombinaciji z gemcitabinom indicirano za zdravljenje bolnikov z metastatskim rakom trebušne slinavke. Pri predpisovanju zdravila Tarceva je treba upoštevati dejavnike, povezane s podaljšanim preživetjem. Koristnega vpliva na podaljšanje preživetja niso dokazali za bolnike z lokalno napredovalo boleznijo.
Odmerjanje in način uporabe: Zdravljenje z zdravilom Tarceva mora nadzorovati zdravnik z izkušnjami pri zdravljenju raka. Zdravilo Tarceva vzamemo najmanj eno uro pred zaužitjem hrane ali dve uri po tem. Kadar je potrebno odmerek prilagoditi, ga zmanjšujemo v korakih po 50 mg. Pri sočasnem jemanju substratov in modulatorjev CYP3A4 bo morda potrebna prilagoditev odmerka. Pri dajanju zdravila Tarceva bolnikom z jetrno okvaro je potrebna previdnost. Če se pojavijo hudi neželeni učinki pride v poštev zmanjšanje odmerka ali prekinitev zdravljenja z zdravilom Tarceva. Uporaba zdravila Tarceva pri bolnikih s hudo jetrno ali ledvično okvaro ter pri otrocih ni priporočljiva. Bolnikom kadilcem je treba svetovati, naj prenehajo kaditi, saj so plazemske koncentracije erlotiniba pri kadilcih manjše kot pri nekadilcih. Nedrobnocelični rak pljuč: Priporočeni dnevni odmerek zdravila Tarceva je 150 mg. Rak trebušne slinavke: Priporočeni dnevni odmerek zdravila Tarceva je 100 mg, v kombinaciji z gemcitabinom. Pri bolnikih, pri katerih se kožni izpuščaj v prvih 4 do 8 tednih zdravljenja ne pojavi, je treba ponovno pretehtati nadaljnje zdravljenje z zdravilom Tarceva.
Kontraindikacije: Huda preobčutljivost za erlotinib ali katero koli pomožno snov.
Posebna opozorila in previdnostni ukrepi: Močni induktorji CYP3A4 lahko zmanjšajo učinkovitost erlotiniba, močni zaviralci CYP3A4 pa lahko povečajo toksičnost. Sočasnemu zdravljenju s temi zdravili se je treba izogibati. Bolnikom, ki kadijo, je treba svetovati, naj prenehajo kaditi, saj so plazemske koncentracije erlotiniba pri kadilcih zmanjšane v primerjavi s plazemskimi koncentracijami pri nekadilcih. Verjetno je, da je velikost zmanjšanja klinično pomembna. Pri bolnikih, pri katerih se akutno pojavijo novi in/ali poslabšajo nepojasnjeni pljučni simptomi, kot so dispneja, kašelj in vročina, je zdravljenje z zdravilom Tarceva treba prekiniti, dokler ni znana diagnoza. Bolnike, ki se sočasno zdravijo z erlotinibom in gemcitabinom, je treba skrbno spremljati zaradi možnosti pojava toksičnosti, podobni intersticijski pljučni bolezni. Če je ugotovljena intersticijska pljučna bolezen, zdravilo Tarceva ukinemo in uvedemo ustrezno zdravljenje. Pri približno polovici bolnikov, ki so se zdravili z zdravilom Tarceva, se je pojavila driska. Zmerno do hudo drisko zdravimo z loperamidom. V nekaterih primerih bo morda potrebno zmanjšanje odmerka. V primeru hude ali dolgotrajne driske, navzeje, anoreksije ali bruhanja, povezanih z dehidracijo, je zdravljenje z zdravilom Tarceva treba prekiniti in dehidracijo ustrezno zdraviti. O hipokaliemiji in ledvični odpovedi so poročali redko. Posebno pri bolnikih z dejavniki tveganja (sočasno jemanje drugih zdravil, simptomi, bolezni ali drugi dejavniki, vključno z visoko starostjo) moramo, če je driska huda ali dolgotrajna oziroma vodi v dehidracijo, zdravljenje z zdravilom Tarceva prekiniti in bolnikom zagotoviti intenzivno intravensko rehidracijo. Dodatno je treba pri bolnikih s prisotnim tveganjem za razvoj dehidracije spremljati ledvično delovanje in serumske elektrolite, vključno s kalijem. Pri uporabi zdravila Tarceva so poročali o redkih primerih jetrne odpovedi. K njenemu nastanku je lahko pripomogla predhodno obstoječa jetrna bolezen ali sočasno jemanje hepatotoksičnih zdravil. Pri teh bolnikih je treba zato premisliti o rednem spremljanju jetrnega delovanja. Dajanje zdravila Tarceva je treba prekiniti, če so spremembe jetrnega delovanja hude. Bolniki, ki prejemajo zdravilo Tarceva, imajo večje tveganje za razvoj perforacij v prebavilih, ki so jih opazili občasno. Pri bolnikih, ki sočasno prejemajo zdravila, ki zavirajo angiogenezo, kortikosteroide, nesteroidna protivnetna zdravila (NSAID) in/ali kemoterapijo na osnovi taksanov, ali so v preteklosti imeli peptični ulkus ali bolezen divertiklov, je tveganje večje. Če pride do tega, je treba zdravljenje z zdravilom Tarceva dokončno ukiniti. Poročali so o primerih kožnih bolezni z mehurji in luščenjem kože, vključno z zelo redkimi primeri, ki so nakazovali na Stevens-Johnsonov sindrom/toksično epidermalno nekrolizo in so bili v nekaterih primerih smrtni. Zdravljenje z zdravilom Tarceva je treba prekiniti ali ukiniti, če se pri bolniku pojavijo hude oblike mehurjev ali luščenja kože. Zelo redko so poročali o primerih perforacije ali ulceracije roženice; opazili so tudi druge očesne bolezni. Zdravljenje z zdravilom Tarceva je treba prekiniti ali ukiniti, če se pri bolnikih pojavijo akutne očesne bolezni, kot je bolečina v očeh, ali se le-te poslabšajo. Tablete vsebujejo laktozo in jih ne smemo dajati bolnikom z redkimi dednimi stanji: intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze.
Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Erlotinib se pri ljudeh presnavlja v jetrih z jetrnimi citokromi, primarno s CYP3A4 in v manjši meri s CYP1A2. Presnova erlotiniba zunaj jeter poteka s CYP3A4 v črevesju, CYP1A1 v pljučih in CYP1B1 v tumorskih tkivih. Z zdravilnimi učinkovinami, ki se presnavljajo s temi encimi, jih zavirajo ali pa so njihovi induktorji, lahko pride do interakcij. Erlotinib je srednje močan zaviralec CYP3A4 in CYP2C8, kot tudi močan zaviralec glukuronidacije z UGT1A1 *in vitro*. Pri kombinaciji ciprofloksacina ali močnega *zaviralca CYP1A2* (npr. fluvoksamina) z erlotinibom je potrebna previdnost. V primeru pojava neželenih dogodkov, povezanih z erlotinibom, lahko odmerek erlotiniba zmanjšamo. Predhodno ali sočasno zdravljenje z zdravilom Tarceva ni spremenilo očistka prototipov *substratov CYP3A4*, midazolama in eritromicina. Inhibicija glukoronidacije lahko povzroči interakcije z zdravili, ki so *substrati UGT1A1* in se izločajo samo po tej poti. Močni *zaviralci aktivnosti CYP3A4* zmanjšajo presnovo erlotiniba in zvečajo koncentracije erlotiniba v plazmi. Pri sočasnem jemanju erlotiniba in močnih zaviralcev CYP3A4 je zato potrebna previdnost. Če je treba, odmerek erlotiniba zmanjšamo, še posebno pri pojavu toksičnosti. Močni *spodbujevalci aktivnosti CYP3A4* zvečajo presnovo erlotiniba in pomembno zmanjšajo plazemske koncentracije erlotiniba. Sočasnemu dajanju zdravila Tarceva in induktorjev CYP3A4 se je treba izogibati. Pri bolnikih, ki potrebujejo sočasno zdravljenje z zdravilom Tarceva in močnim induktorjem CYP3A4 je treba premisliti o povečanju odmerka do 300 mg ob skrbnem spremljanju njihove varnosti. Zmanjšana izpostavljenost se lahko pojavi tudi z drugimi induktorji, kot so fenitoin, karbamazepin, barbiturati ali šentjanževka. Če te zdravilne učinkovine kombiniramo z erlotinibom, je potrebna previdnost. Kadar je mogoče, je treba razmisliti o drugih načinih zdravljenja, ki ne vključujejo močnega spodbujanja aktivnosti CYP3A4. Bolnikom, ki jemljejo varfarin ali druge *kumarinske antikoagulante*, je treba redno kontrolirati protrombinski čas ali INR. Sočasna uporaba *zaviralcev P-glikoproteina*, kot sta ciklosporin in verapamil, lahko vodi v spremenjeno porazdelitev in/ali spremenjeno izločanje erlotiniba. Za erlotinib je značilno zmanjšanje topnosti pri pH nad 5. *Zdravila, ki spremenijo pH v zgornjem delu prebavil*, lahko spremenijo topnost erlotiniba in posledično njegovo biološko uporabnost. Učinka antacidov na absorpcijo erlotiniba niso proučevali, vendar je ta lahko zmanjšana, kar vodi v nižje plazemske koncentracije. Kombinaciji erlotiniba in zaviralca protonske črpalke se je treba izogibati. Če menimo, da je uporaba antacidov med zdravljenjem z zdravilom Tarceva potrebna, jih je treba jemati najmanj 4 ure pred ali 2 uri po dnevnem odmerku zdravila Tarceva. Če razmišljamo o uporabi ranitidina, moramo zdravili jemati ločeno: zdravilo Tarceva je treba vzeti najmanj 2 uri pred ali 10 ur po odmerku ranitidina. V študiji faze Ib ni bilo pomembnih učinkov *gemcitabina* na farmakokinetiko erlotiniba, prav tako ni bilo pomembnih učinkov erlotiniba na farmakokinetiko gemcitabina. Erlotinib poveča koncentracijo platine. Pomembnih učinkov *karboplatina* ali paklitaksela na farmakokinetiko erlotiniba ni bilo. *Kapecitabin* lahko poveča koncentracijo erlotiniba. Pomembnih učinkov erlotiniba na farmakokinetiko kapecitabina ni bilo.
Neželeni učinki: *Zelo pogosti neželeni učinki* so kožni izpuščaj in driska, kot tudi utrujenost, anoreksija, dispneja, kašelj, okužba, navzeja, bruhanje, stomatitis, bolečina v trebuhu, pruritus, suha koža, suhi keratokonjunktivitis, konjunktivitis, zmanjšanje telesne mase, depresija, glavobol, nevropatija, dispepsija, flatulenca, alopecija, okorelost, pireksija. *Pogosti neželeni učinki* so gastrointestinalne krvavitve, krvavitev iz nosu, nenormalnosti testov jetrne funkcije, keratitis, zanohtnica. *Redko* so poročali o jetrni odpovedi. *Občasno* pa o perforacijah v prebavilih, poraščenosti moškega tipa pri ženskah, spremembah obrvi, krhkih nohtih, odstopanju nohtov od kože, blagih reakcijah na koži (npr. hiperpigmentacija), spremembah trepalnic, resni intersticijski pljučni bolezni, vključno s smrtnimi primeri. *Zelo redko* so poročali o primerih, ki so nakazovali na Stevens-Johnsonov sindrom/toksično epidermalno nekrolizo in so bili v nekaterih primerih smrtni, ter o ulceracijah in perforacijah roženice.
Režim izdaje zdravila: H/Rp. **Imetnik dovoljenja za promet:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, Velika Britanija. **Verzija:** 2.0/09. **Informacija pripravljena**: september 2009.

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1. RELISTOR® - Povzetek glavnih značilnosti zdravila; **2.** Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. New York, NY: McGraw-Hill; 2006:547-590. **3.** RELISTOR™ methylnatrexone bromide: subcutaneous injection. Product Monograph – september 2008.

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Dent RAG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

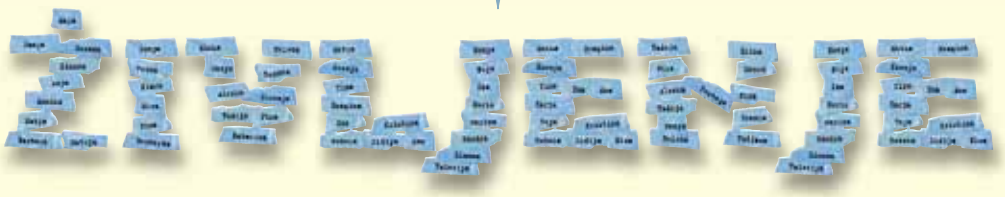
Chapman S, Nakielny R. *A guide to radiological procedures.* London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

Page proofs will be faxed or sent by E-mail to the corresponding author. It is their responsibility to check the proofs carefully and fax a list of essential corrections to the editorial office within 48 hours of receipt. If corrections are not received by the stated deadline, proof-reading will be carried out by the editors.

AROMASIN®
eksemestan

Endokrino zdravljenje bolnic z rakom dojk po menopavzi



BISTVENE INFORMACIJE IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

AROMASIN® 25 mg obložene tablete

Sestava in oblika zdravila: obložena tableta vsebuje 25 mg eksemestana. **Indikacije:** Adjuvantno zdravljenje žensk po menopavzi, ki imajo invazivnega zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji in so se uvodoma vsaj 2 do 3 leta zdravile s tamoksifenom. Zdravljenje napredovalega raka dojke pri ženskah z naravno ali umetno povzročeno menopavzo, pri katerih je bolezen napredovala po antiestrogenskem zdravljenju. Učinkovitost še ni bila dokazana pri bolnicah, pri katerih tumorske celice nimajo estrogenskih receptorjev. **Odmerjanje in način uporabe:** 25 mg enkrat na dan, najbolje po jedi. Pri bolnicah z zgodnjim rakom dojke je treba zdravljenje nadaljevati do dopolnjenega petega leta adjuvantnega hormonskega zdravljenja oz. do recidiva tumorja. Pri bolnicah z napredovalim rakom dojke je treba zdravljenje nadaljevati, dokler ni razvidno napredovanje tumorja. **Kontraindikacije:** znana preobčutljivost na učinkovino zdravila ali na katero od pomožnih snovi, ženske pred menopavzo, nosečnice in doječe matere. **Posebna opozorila in previdnostni ukrepi:** predmenopavzni endokrini status, jetrna ali ledvična okvara, bolniki z redko dedno intoleranco za fruktozo, malabsorpcijo glukoze/galaktoze ali pomanjkanjem saharoza-izomaltaze. Lahko povzroči alergijske reakcije ali zmanjšanje mineralne gostote kosti ter večjo pogostnost zlomov. Ženskam z osteoporozo ali tveganjem zanjo je treba na začetku zdravljenja izmeriti mineralno kostno gostoto s kostno denzitometrijo. Čeprav še ni dovolj podatkov, kako učinkujejo zdravila za zdravljenje zmanjšane mineralne kostne gostote, ki jo povzroča Aromasin, je treba pri bolnicah s tveganjem uvesti zdravljenje ali profilakso osteoporoze ter bolnice natančno spremljati. **Medsebojno delovanje z drugimi zdravili:** Sočasna uporaba zdravil – npr. rifampicina, antiepileptikov (npr. fenitoina ali karbamazepina) ali zdravil rastlinskega izvora s šentjaževko – ki inducirajo CYP 3A4, lahko zmanjša učinkovitost Aromasina. Uporabljati ga je treba previdno z zdravili, ki se presnavljajo s pomočjo CYP 3A4 in ki imajo ozek terapevtski interval. Kliničnih izkušenj s sočasno uporabo zdravila Aromasin in drugih zdravil proti raku ni. Ne sme se jemati sočasno z zdravili, ki vsebujejo estrogen, saj bi ta izničila njegovo farmakološko delovanje. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Po uporabi zdravila je lahko psihofizična sposobnost za upravljanje s stroji ali vožnjo avtomobila zmanjšana. **Neželeni učinki:** neželeni učinki so bili v študijah, v katerih so uporabljali standardni odmerek 25 mg, ponavadi blagi do zmerni. *Zelo pogosti (> 10 %):* vročinski oblivi, bolečine v sklepih, mišicah in kosteh, utrujenost, navzea, nespečnost, glavobol, močnejše znojenje, ginekološke motnje. **Način in režim izdajanja:** zdravilo se izdaja le na recept, uporablja pa se po navodilu in pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Luksembourg SARL, 283, route d'Arlon, L-8011 Strassen, Luksemburg. **Datum zadnje revizije besedila:** 11.4.2008
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Pfizer

Pfizer Luxembourg SARL, Grand Duchy of Luxembourg, 51, Avenue J.F. Kennedy, L-1855,
PFIZER, Podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Letališka 3c, 1000 Ljubljana, SLOVENIJA

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