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ALIMTA®
pemetreksed

Pravi **Izbor**
Pravi **Bolnik**
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:** Pemetrekseda 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 zaploditev 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 daljšimi 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 posameznimi 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 nevtrofili/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 nevtrofili/granulociti, znižani levkocitit, 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 nevtrofili/granulociti, znižani levkocitit, 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 nevtrofili, 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 intersticijske 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 5, NL 3991 RA, Houten, Nizozemska. Datum zadnje revizije besedila 24.10.2009. **Način in režim izdajanja zdravila:** H
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review

Urine and bladder washing cytology for detection of urothelial carcinoma: standard test with new possibilities

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Background. Light microscopic evaluation of cell morphology in preparations from urine or bladder washing containing exfoliated cells is a standard and primary method for the detection of bladder cancer and also malignancy from other parts of the urinary tract. The cytopathologic examination is a valuable method to detect an early recurrence of malignancy or new primary carcinoma during the follow-up of patients after the treatment of bladder cancer.

Conclusions. Characteristic cellular and nuclear signs of malignancy indicate invasive or *in situ* urothelial carcinoma or high-grade papillary urothelial carcinoma. However, low sensitivity of the method reflects the unreliable cytopathologic diagnosis of low-grade urothelial neoplasms as cellular and nuclear signs of malignancy in these neoplasms are poorly manifested. Many different markers were developed to improve the diagnosis of bladder carcinoma on urinary samples. UroVysion™ test is among the newest and most promising tests. By the method of *in situ* hybridization one can detect specific cytogenetic changes of urothelial carcinoma.

Key words: cytology; urine; bladder washing; urothelial carcinoma

Introduction

The examination of urine is one of the oldest medical procedures dating back to the Old Egypt.[1,2] First microscopical examination of the cells in the urinary sediment was reported by the Czech doctor Lambl back in 1856.[2]

At present the cytopathological examination of urine or other fluid samples from the urinary tract is a routine noninvasive diagnostic procedure to detect cancer of the urinary tract, foremost bladder cancer especially in patients with painless haematuria.[3,4] It is also used during the follow-up procedures of the patients previously treated for bladder cancer in order to early detect recurrence or new primary.[4] Exceptionally, the cytopathological examination of urine is used for the screening for urothelial carcinoma in the high risk population.

The cytopathological examination is a highly specific method for the diagnosis of invasive and *in situ* urothelial carcinoma and high-grade papillary carcinoma, however it is notorious of being unreliable for the detection of low-grade papillary neoplasms.[5,6]

Preparation of fluid samples from the urinary tract for cytopathological examination

A most common sample from the urinary tract is spontaneous – voided urine. Bladder washing samples are also very frequent samples sent to the cytology laboratory. Other samples such as catheterized urine or urine obtained by the retrograde catheterization of urethers or renal pelvis are sent for the cytopathological examination only occasionally.

The second morning voided urine is the most appropriate sample for the cytopathological examination as it contains enough of preserved cells. The first morning urine contains more cells but they show different degrees of degeneration being exposed to the acid milieu of urine through the

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TABLE 1. Cytological-histological correlation in 125 cases of urines and bladder washings with subsequent tissue biopsy from 2007 to 2009

DIAGNOSIS Cytology / Histology	Negative	Mild atypia	Atypia NOS*	Suspicious for carcinoma	Carcinoma	Total
LG** papillary urothelial carcinoma	5	4	8	9	2	28
HG*** papillary urothelial carcinoma	1	-	-	4	17	22
Invasive urothelial carcinoma	-	1	2	2	21	26
Invasive and in situ urothelial carcinoma	-	-	-	-	2	2
In situ urothelial carcinoma	-	-	1	3	7	11
No malignancy	21	4	2	8	1	36
Total	27	9	13	26	50	125

* NOS = not otherways specified; **LG = low-grade; ***HG = high-grade

night and are less suitable for the cytological evaluation. Because the cells exfoliate from the urothelium intermittently, three urine samples should be examined from three consecutive days to ensure that diagnostic cells were sampled.[2]

The bladder washing sample is obtained during or prior cystoscopy which is an invasive diagnostic procedure for the macroscopical evaluation of the bladder mucosa. First the bladder should be emptied by a catheter. Then 50 to 100 ml of normal saline is instilled and recovered and this procedure is repeated three times.[2] Bladder washing exfoliates large sheets of urothelium and even three-dimensional urothelial fragments. Therefore, bladder washing samples are highly cellular and contain well preserved cells.

When fluid samples cannot be delivered to the cytology laboratory within three hours after they were obtained, they can be prefixed with a mixture of 2% polyethylen glycol (Carbowax™) and 50% to 70% ethanol.

Different techniques are used for the cytopathological preparation of fluid samples of the urinary tract. Some laboratories still use a centrifugation of fluid and then the pellet is directly smeared onto the glass slide. Other laboratories introduced the commercial ThinPrep™ technique for the preparation of samples from the urinary tract.[7] ThinPrep™ was first developed for the preparation of cervical cytology samples. The membrane filtration technique is used in several laboratories including ours. Urine or bladder washing sample is filtered through the polycarbonate membrane filter with 5 μm pores (Costar® filter system, Costar Europe Ltd., Netherlands, Europe; Nucleopore® filter, diameter 47 mm, pores 5 μm, Whatman Inc., New Jersey, USA), so predominantly urothelial cells remain on the filter. Usually the majority of erytrocytes and leukocytes are removed because the gentle negative pressure is applied to assist filtration, which deforms these cells so they pass through the filter. The cell monolayers are obtained by gently imprinting filter onto a pair of glass slides. The cell sample on the slide should be fixed by the immediate immersion into Delaunay fixative (acetone: 96% ethanol 1:1 + 0.5 ml/l trichoracetic acid) or fixed by spraying with Merckofix® (Merck KGaA, Darmstadt, Germany). Cell preparations are subsequently stained by the Papanicolaou method.

Cytopathological diagnosis of urothelial tumours

The last WHO classification of the tumours of the urinary system (published in 2004) divides urothelial neoplasms into infiltrating (invasive) urothelial carcinomas and non-invasive urothelial carcinomas.[8,9] Later they are further subdivided into low and high-grade papillary carcinomas, papillary urothelial neoplasms of low malignant potential (PUNLMP) and papillomas on one side and urothelial carcinomas *in situ* on the other side.[9]

In his last edition of Diagnostic cytology and its histopathologic bases, Koss suggested that for the purpose of cytopathological evaluation the urothelial carcinomas should be divided into papillary and non-papillary carcinomas.[5] The reason is that cytopathological diagnosis of non-papillary carcinomas, including invasive and *in situ* carcinomas is very reliable (specificity ranging from 88.1 to 99.%, mean 97.1%; our data 96%, Table 1), while the cytopathological evaluation of papillary neoplasms which are often of low-grade is notorious for being of limited usefulness.[5,10-12]

Another obstacle of the cytopathological evaluation is that the true origin of malignant cells found in urine cannot be reliably identified. Malignant

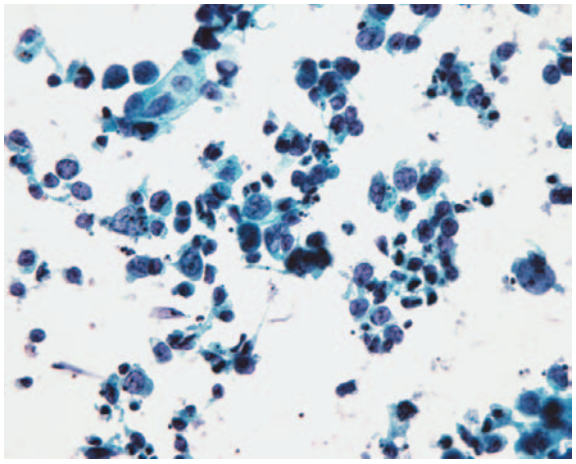

FIGURE 1. Malignant cells of invasive urothelial carcinoma with cellular debris (necrosis) in the background (Papanicolaou, x400).

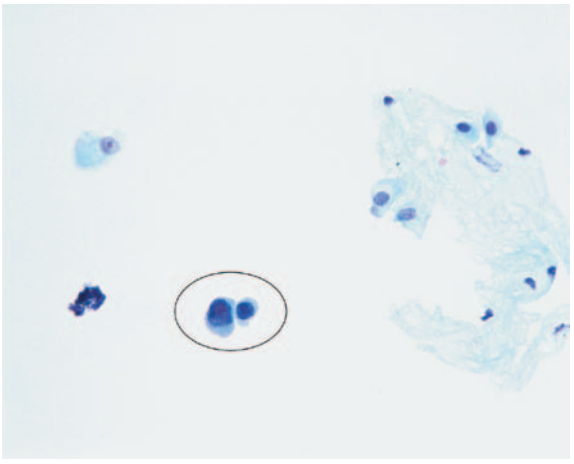

FIGURE 2. Two malignant cells (in circle) of in situ urothelial carcinoma (note: clear background) (Papanicolaou, x400).

cells found in urine can originate not only from bladder, but from any part of the urinary tract, namely from renal pelvis, urether or urethra.

Infiltrating (invasive) urothelial carcinoma

Among non-papillary carcinomas the cells of invasive urothelial carcinomas usually exhibit clear cytological and nuclear characteristics of malignancy in voided urine or bladder washing samples.[5,6,10] Specifically, polymorphous cells with increased nuclear-cytoplasmic ratio, polymorphous nuclei, nuclear hyperchromasia with coarsely granular and unevenly distributed chromatin, and nucleoli are observed (Figure 1). The cellularity of samples partially depends on the type of specimen, namely larger number of malignant cells is found in bladder washing, while the cell degeneration with pyknosis is more pronounced in voided urine samples. Cells lay singly or in poorly cohesive clusters. Background may contain necrotic debris, blood and inflammatory cells. Sensitivity of cytology for the detection of invasive urothelial carcinoma is high (81-100%, our data: 100%, Table 1).[5,10,11]

Urothelial *in situ* carcinoma

Also the urothelial *in situ* carcinoma exfoliates cells with evident malignant morphology, similar to cells of invasive urothelial carcinoma (Figure 2).[5,6] In voided urine samples the cells are of an intermediate size or small, mostly laying singly. Single bizarre cells can be observed. Nuclei are large, of irregular shape, hyperchromatic, contain coarse chromatin, large nucleoli; pyknosis is present frequently. Cytoplasm is scanty. In contrast to invasive urothelial carcinoma, generally no necrosis, scanty erythrocytes or leukocytes are found in the background of samples containing cells of urothelial in situ carcinoma. Due to the obvious morphological signs of malignancy the sensitivity of cytology for the detection of urothelial in situ carcinoma is high (70-100%; our data: 100%, Table 1).[5,10,11] However, it is difficult to tell apart reliably the malignant cells of the *in situ* carcinoma from the cells of invasive carcinoma even when the characteristics of the background are considered in the cytopathological diagnosis.

High-grade papillary urothelial carcinomas

Among papillary tumours, high-grade papillary urothelial carcinomas (including former WHO classification grade II and III) shed cells with cytological atypia consistent with malignancy, as described above. The majority of high-grade carcinomas of former grade III exfoliate evident malignant cells, while in 20-30% of former grade II carcinomas the cytological atypia is less pronounced. Sensitivity of cytology for the detection of high-grade papillary urothelial carcinomas of former grade II and III combined is 72%, however for papillary urothelial carcinomas of former grade III is 91% (our data 94%, Table 1).[5,10,11]

Low-grade papillary urothelial carcinomas and other low-grade papillary neoplasms

On the contrary, low-grade papillary urothelial carcinomas are difficult to diagnose in cell samples, because the cytological signs of malignancy are not obvious.[5,6] Cells and nuclei are rather uni-

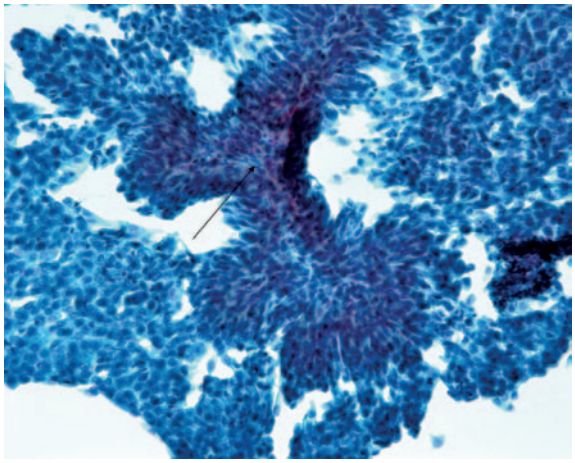

FIGURE 3. Papillary structure covered with mildly atypical urothelial cells diagnostic of low-grade papillary urothelial neoplasm (Papanicolaou, x400).

FIGURE 4. Typical polioma virus cytopathic effect on urothelial cell (Papanicolaou, x400).

form, nuclear-cytoplasmic ratio is not obviously increased. Nuclei are only slightly or moderately enlarged, chromatin is relatively bland. These nuclei are difficult to recognize as malignant in cytology. The background is typically clean, some erythrocytes can be found. Only rarely true papillary fragments containing fibrovascular core can be found, but are not specific for papillary carcinomas; they could belong to PUNLMP or papillomas (Figure 3). Urinary cytology is not reliable for diagnosing low-grade papillary carcinoma and other low-grade papillary neoplasms. Sensitivity for the detection of low-grade papillary tumours is low, however various percentages are reported in the literature ranging from 0-73% (majority between 30 to 40%; our data: sensitivity 18% for the positive diagnosis and 55% for the combined positive/suspicious diagnosis, Table 1).[5,10-13]

Differential diagnosis of inconclusive cytological atypia

In low-grade papillary urothelial carcinomas and other low-grade papillary neoplasms cells exhibit some degree of cytological atypia described above. However, several benign lesions can show similar cytological atypia, namely reactive atypia related to inflammation, stones in the urinary tract or instrumentation.[5,6] Also the post-treatment reactive urothelial changes could be pronounced and have to be taken into consideration. Cytological atypia of reactive type can be very prominent after the irradiation of bladder, intravesical chemotherapy with mitomycin or immunotherapy with Bacillus Calmette-Guérin (BCG) (used for the therapy of carcinoma *in situ*). The polyoma virus infection produces the so called decoy cells with enlarged, usually round nuclei that have typical intranuclear viral inclusions (Figure 4). The chromatin has appearance of ground glass, with condensation of chromatin at the nuclear border, so called type 1 nuclear changes. The cytoplasm of decoy cells is scarce to moderate, thickened or degenerated, may have a comedo shape. Other three types of polyoma related cytological changes are described but are not so reliably recognized in routine setting.[2]

Non-urothelial carcinomas of the urinary tract

In rare instances also non-urothelial malignant cells are observed and can be diagnosed by the cytopathological examination of cell samples from the urinary tract. The most common non-urothelial carcinoma is squamous cell carcinoma.[5] It can exfoliate cells with obvious squamous features, namely orangeophylic cytoplasm that is well demonstrated in Papanicolaou stained cell preparations. When combined with malignant cytological features the diagnosis of squamous cell carcinoma can be made on urine or bladder washing sample. However, it is difficult if not impossible to differentiate whether malignant squamous cells originate from squamous cell carcinoma of bladder or they belong to the part of urothelial carcinoma of bladder with squamous differentiation. One also has to bear in mind that in the urinary samples from female patients the malignant squamous cells could originate from squamous cell carcinoma of the uterine cervix with exfoliated cells in the vaginal excretions washed by urine or by direct invasion of squamous cell cervical carcinoma into the bladder.

In males, adenocarcinoma of the prostate can exfoliate cells into the urine, occasionally they are found in bladder washings.[5] Roundish glandular like structures of malignant cells can be found, with the cytological atypia roughly reflecting the grade of prostate adenocarcinoma. Immunocytochemical staining with antibody to prostate specific antigen (PSA) can confirm the final diagnosis of prostatic adenocarcinoma.

Ancillary urine-based techniques for the diagnosis of urothelial bladder cancer

Although the cytopathological examination of urine or bladder washing cell samples is very specific (97%; our data: 96%, Table 1) it suffers from low sensitivity especially in the case of low-grade papillary tumours.[5,10-13] This type of tumours is prone to recurrence and it is found in 70% of patients, furthermore 5% of them develop invasive carcinoma.[13] A specific clinical problem are patients with early invasion into *lamina propria* at first diagnosis. In these patients the disease progresses to the muscular invasive form in 20-30% of cases and the progression potentially leads to a fatal outcome.[13] The patients treated previously for urothelial carcinoma are therefore followed-up regularly with cystoscopy and cytology. Due to the above mentioned limitations of cytology the need for new non-invasive techniques to detect recurrences has emerged.[13] However, although the new markers exhibit better sensitivity than cytology only few could reach the high specificity of cytology.

DNA ploidy

In the seventies and eighties of the last century the researchers and pathologists were using DNA cytometry to measure DNA ploidy of urothelial tumors.[14,15]

There was found that the non-invasive low-grade urothelial tumours were predominantly diploid, while grade II urothelial carcinomas were diploid in about 50% of cases while the other 50% were aneuploid. The grade III tumours and carcinomas *in situ* were predominantly aneuploid. When correlating the DNA ploidy to clinical data they found that aneuploid tumours were associated with tumour persistence, recurrence, and progression to invasion.[16] However, DNA diploidy in low-grade tumours could not improve the prediction of recurrence which is very frequent in these tumours. DNA ploidy measurement in urothelial tumours has reached its limitations, so new ancillary methods were searched for.

ImmunoCyt/uCyt™

This cytology based test was developed in 1997. It is an immunofluorescence based test, using three monoclonal antibodies, two of them (M344 and LDQ10, labelled with fluorescein green) are directed against mucin-like antigens related to urothelial carcinoma.[17,18] They were found to be positive in 71% of non-invasive (pTa) or early invasive (pT1) tumours. The third antibody (19A211 labelled with Texas red) is directed against high molecular weight carcinoembrionic antigen (CEA). It was found to be positive in 90% of non-invasive (pTa) or early invasive (pT1) tumours. Sensitivity of the test was shown to be 53-100% (mean 90%) also for low-grade tumours, while the specificity was 64-95% (74%), which is less than cytology. The test obtained FDA clearance in 2000 for the detection of malignant cells in urine in patients treated for urothelial cancer.

BTA stat®

Bard BTA stat® (bladder tumour antigen test)® (Polymedco, Cortland Manor, NY, USA) is a soluble urine marker test that was aimed at the basal membrane antigen detection (complement factor H-related protein) in the urine using latex agglutination test (immunoassay).[13] The test showed variable sensitivity (34%-100%) and especially its sensitivity for low-grade tumours was rather modest, while the specificity was in the same range (40-96%). However, the high false positive rate (4-34%) makes the test debatable for a wider clinical use. FDA approved the test to detect bladder cancer in voided urine.

NMP22 (nuclear matrix protein)™ immunoassay

NMP22™ test (Matritech, Newton, MA, USA) is a soluble urine marker test. NMP22 (nuclear matrix protein) is a member of family of nuclear matrix proteins that are involved in DNA configuration, structure and function.[13,19,20] It was shown that the sufficient difference existed between normal and urothelial cancer cells to be used as a diagnostic test. The NMP22™ detection method is an immunoassay that showed high sensitivity (60-86%) for the detection of urothelial neoplasia, however the specificity is bellow that of cytology (48-81%) producing many false positive tests. Besides, the test

TABLE 2. Results of the first set of the UroVysion™ test in patients with different cytopathological diagnoses on cell samples.

		FISH UroVysion™ test		
		Negative	Positive	Total
Cytology	No malignancy (negative)	1	-	1
	Mild Atypia	1	1	2
	Moderate atypia / suspicious for carcinoma	-	5	5
	Carcinoma (positive)	-	3	3
	Total	2	9	11

FISH = fluorescence *in situ* hybridization

was reported to be rather inconvenient and costly. Anyhow, the FDA approved to detect bladder cancer in voided urine, adjunct to cystoscopy.

Other potential urinary markers of urothelial carcinoma

Many other markers either cell based (microsatellite analysis, telomerase detection, Quanticyt nuclear karyometry) or soluble urine markers (BLCA-4, BLCA-1, HA-HAse, survivin) were reported to be useful for the detection of urothelial cancer.[13] The majority exhibited higher sensitivity than cytology, however they didn't reach the high specificity of cytology and did not obtain the FDA approval for the clinical use.

Multitarget multicolour fluorescence *in situ* hybridization (FISH) UroVysion™ test

High frequency of specific chromosomal abnormalities in urothelial cancers was found in the nineties and several DNA probes were made to detect these abnormalities.[21,22] Initial studies tested single DNA probes using FISH for the detection of urothelial carcinoma, however single probes resulted in limited specificity and sensitivity. The procedures were also time consuming, therefore they could be not introduced into the routine clinical management of the patients.

The study of Sokolova *et al.* showed that the application of several DNA probes combined significantly increased the sensitivity for the detection of abnormal cells.[23] In their study they tested ten FISH probes and found that the highest sensitivity was achieved using three chromosome enumeration probes (CEP), namely for chromosome 3 (labelled by Spectrum red), chromosome 7 (labelled by Spectrum green), chromosome 17 (labelled by Spectrum aqua) and one locus-specific identifier (LSI) probe for 9p21 (labelled by Spectrum gold). In their study the cut-off value set at 5 abnormal cells yielded sensitivity 84%, specificity 92% for the detection of urothelial carcinoma. Based on their observation the commercially available multicolour multitarget FISH UroVysion™ test (Abbott Molecul Inc., Des Plaines, IL, USA) incorporating all four DNA probes was made.[24] Initially it was FDA approved in 2001 for the surveillance of patients with bladder cancer, later it was approved also for the detection of bladder cancer in persons with haematuria suspected of having bladder cancer. In other words, UroVysion™ can be used for screening of bladder cancer in patients with haematuria.

Already in 2002 the studies using commercial UroVysion™ test were published. One of the first was the study by Bubendorf *et al.* who showed that UroVysion™ could facilitate the diagnosis of bladder cancer and detect the recurrence.[25] They claimed that the test was a rapid, simple and powerful diagnostic method. Either voided urine or bladder washing samples prepared as cytospins could be used. They found that the sensitivity for the detection of non-invasive carcinoma was 73%, while later studies showed sensitivity ranging from 36-86%. The sensitivity for the detection of invasive carcinoma was even higher reaching 100%, and other studies confirmed 94-100% sensitivity. The specificity in their study was 96%, in the later studies up to 100%.[26-29] They suggested that the cystoscopy examination should follow a positive test even in the absence of suspicious or positive cytology. Although the test is rather expensive, the cost benefit ratio was supposedly lower taking into account the decreased need for the diagnostic cystoscopy.

In one of the later studies Yoder *et al.* suggested that if cytology was positive and used as the first diagnostic test no UroVysion™ test was needed, as cytology is nearly 100% specific.[26] If cytology was negative or atypical cells were found, the reflex UroVysion™ test was performed on the same urine or bladder washing specimen. The problem arose if FISH was positive and the subsequent cys-

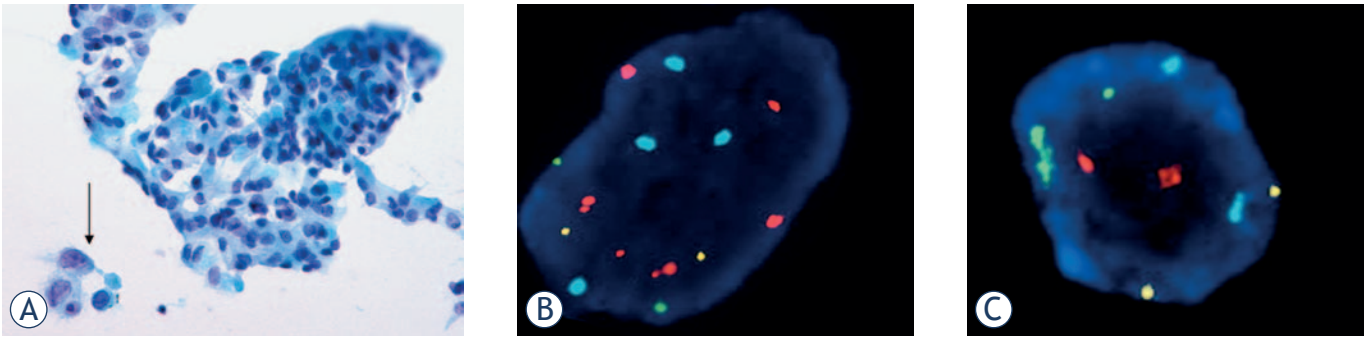

FIGURE 5. Mild cytological atypia of urothelial cells (arrow) in routine cytology bladder washing specimen (Papanicolaou, x400) (A). Positive UroVysion test: 9 aneuploid cells (B). Majority were diploid cells (C).

toscopy was negative. The authors found that these were anticipatory positive cases because 50 to 80% patients with FISH positive test developed cancer within 29 months.

In one of the last published studies using UroVysion™ test, Kipp *et al.* have shown that also the percentage of polysomic cells (cells having an extra copy of one or more chromosomes) in the FISH positive patients is important.[27] The result of more than 5% of abnormal cells correlated with the recurrence and the progression of urothelial carcinoma to muscle invasion in patients with non-(muscle)-invasive carcinoma. Furthermore, the result of more than 31% of abnormal cells was correlated to muscle invasion. However, a similar problem appeared as in previous studies, many patients with FISH positive test had negative cystoscopy, so the further treatment of these patients would have to be determined.

Obviously, as any diagnostic test also the UroVysion™ FISH test could give false positive results, namely signal splitting, few tetrasomic cells (cells of the G2M phase) or overlapping cells could be interpreted as polysomic cells.

On the other hand the test could also be false negative, specifically if there are no diagnostic cells in the sample or due to certain technical problems. As in other diagnostic tests, including cytology, it was also found to be negative in some low-grade urothelial tumours.

Nevertheless, there is a general agreement among cytopathologists that UroVysion™ FISH test is a new promising diagnostic tool in urinary cytology.[28,29]

Experience of the Institute of Pathology, Faculty of Medicine, University of Ljubljana with UroVysion™ test

We started introducing UroVysion™ test by the end of 2008. The performance of the UroVysion™ test on a Papanicolaou stained slides of urine or bladder washings prepared by membrane filter imprint technique routinely used at our institute, was not yet reported.

Our approach was to find the area on the slide containing well preserved and well distributed atypical /representative cells which were marked by a diamond pencil for the subsequent testing by UroVysion™. UroVysion™ test was performed according to the manufacturer's guidelines with two minor adjustments, the slides were first decolorized in acid ethanol and the enzyme digestion was lengthened to 28 minutes. Eighteen out of 29 tests were used to introduce and optimize a new method and further, eleven tests were used on diagnostic samples (Table 2). We found that all 5 cases of undetermined and suspicious atypia were UroVysion™ test positive, while also one case of mild cytological atypia that would be regarded as negative/benign was positive in a patient who was previously treated for non-invasive low-grade papillary carcinoma (Figure 5). As expected all 3 cases with positive/malignant cytology were UroVysion™ test positive and one case with negative cytology was also negative on UroVysion™ test. We concluded that the cytopathological diagnosis could be improved in 6/7 (88%) of atypical-suspicious cases. However, further experience with the test will be needed and the correlation of the UroVysion™ test results to histopathological diagnosis on tissue biopsies is awaited in order to improve the diagnosis in increasing number of patients with urothelial carcinoma in Slovenia.[30]

Our initial impression is that the UroVysion™ test requires optimization to suit the procedures already used in one's laboratory for the preparation of the fluid samples from the urinary tract. The introduction of UroVysion™ test requires initial staff training and additional equipment, foremost fluorescence microscope with appropriate filters. At the present the test is rather costly and time consuming.

Conclusions

Malignant cytomorphological characteristics of exfoliated cells in urine or bladder washing can facilitate the diagnosis of primary or recurrent urothelial carcinoma, therefore the method remains a useful diagnostic test with high specificity. However, in cases with less pronounced cellular and nuclear atypia the cytopathological diagnosis is not reliable giving too many false negative results. Many ancillary tests were developed on urinary samples in the past two decades to overcome the low sensitivity of cytology for the detection of bladder cancer. The newest and most promising test is commercially available multicolour multitarget FISH UroVysion™ test which was introduced into routine diagnostics also at the Institute of Pathology, Faculty of Medicine, University of Ljubljana.

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research article

Imaging findings in bisphosphonate-induced osteonecrosis of the jaws

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Background. Bisphosphonates are drugs used in the treatment of lytic bone metastases, multiple myeloma, hypercalcemia of malignant origin, osteoporosis, and diseases such as Paget's disease. Recently osteonecrosis of the jaw has been associated with the use of bisphosphonates. This study describes the imaging findings of bisphosphonate-associated osteonecrosis of the jaws.

Patients and methods. Eleven patients, receiving bisphosphonate medication for approximately 28 months, with pain on affected side, nonhealing extraction sockets, purulent discharge and swelling in soft tissue were examined. Imaging consisted of non-contrast enhanced CT and contrast enhanced MRI. All patients underwent surgery of affected bone and histology confirmed osteonecrosis.

Results. CT scan showed osteolytic and sclerotic lesions with cortical bone destruction in all patients. The osteonecrosis was identified as delimited focal lesions with reduction of the signal on T1- weighted imaging and T2- weighted imaging. All the patients had soft-tissue involvement with enhancement in orbicular, buccinator muscle of the mouth or masticator space and adenopathy in submandibular and jugular digastric chain.

Conclusions. Bisphosphonate related osteonecrosis of the jaw presents a variety of imaging findings that help to determine the extent of the disease and track the progression, however they are not specific for this disease.

Key words: bisphosphonates; osteonecrosis; jaw; CT; MRI

Introduction

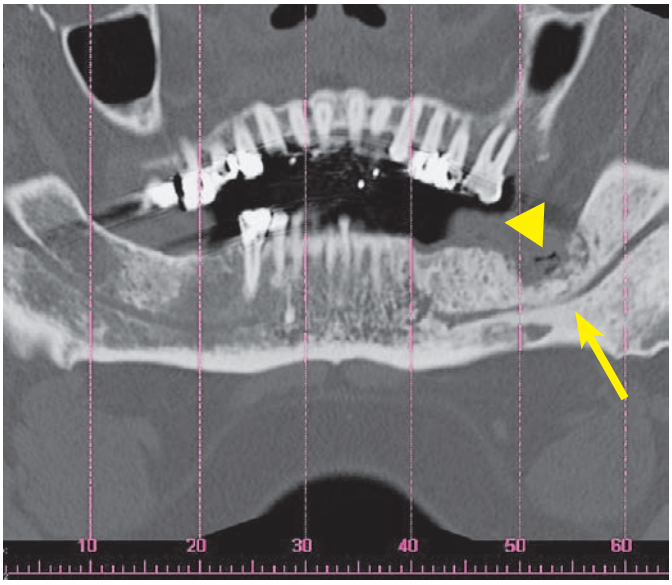
Bisphosphonates are drugs used in the treatment of lytic bone metastases, multiple myeloma, hypercalcaemia of malignant origin, osteoporosis, and diseases such as Paget's disease.[1,2] Bisphosphonates which decrease bone turnover by inhibiting osteoclast mediated bone resorption are providing a significant improvement in the symptoms as a result of reducing pain, bone demineralization, and bone fractures, either pathologic or due to insufficiency.[2,3] Given the prevalence of these diseases, bisphosphonates are one of the most prescribed drug groups in the world, particularly in patients with high incidence cancer and frequent bone metastases.[1,2,4,5] Recently osteonecrosis of mandibula and maxilla has been associated with the use of bisphosphonates.[6-10]

Such patients are referred to radiological institutes for the evaluation of bisphosphonate-induced changes in their jaws, the exclusion of other diseases of the jaws (infected osteoradionecrosis, chronic osteomyelitis or pathological fractures) and the evaluation of the jaws before orofacial procedures.[10]

The objective of this study was to examine the use of CT and MRI in the assessment of bone lesions caused by this disease.

Patients and methods

Eleven patients, 6 men and 5 women, mean age 52 years (range 41- 76 years) who were treated with bisphosphonates were prospectively examined. They were referred to the Department of the



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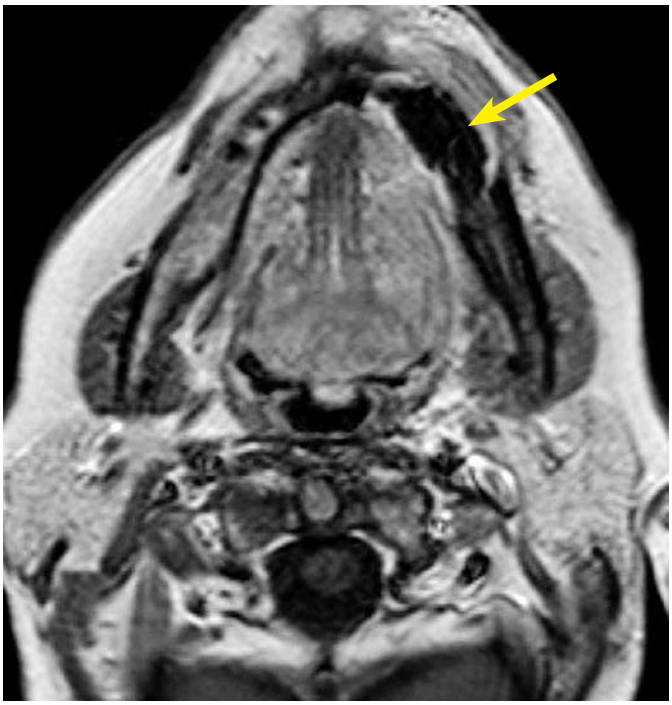

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FIGURE 1. CT and MRI image of a 62-year-old woman with multiple myeloma and histologically proved bisphosphonate-induced osteonecrosis. (A) Panoramic CT reconstruction shows the osteolytic region on the left side (arrow head) as well as sclerosis of the bone marrow with involvement of the inferior alveolar canal (arrow). (B) The axial T1-weighted, contrast enhanced, MRI shows an enhancement at the periphery of the necrotic mandibular region and sequestration of mandibula (arrow).

Maxillofacial and Oral Surgery with pain on affected side, nonhealing extraction sockets, purulent discharge and swelling in soft tissue.

The indication for treatment with bisphosphonates was multiple myeloma in 6 patients (55%), breast cancer bone metastases in 3 patients (27%) and prostate cancer bone metastases in 2 patients (18%).

TABLE 1. Findings in CT imaging of the jaws of 11 patients with bisphosphonate-induced osteonecrosis of the jaws

Findings in CT images	Number of patients
Sclerotic changes	11
Osteolytic changes	11
Periostal bone proliferation	7
Sequestration	1
Inferior alveolar canal involvement	4

Nine patients were treated with zolendronic acid and two with zolendronic and pamidronic acid. The patients had taken bisphosphonate medication for approximately 28 months (range: 13- 36 months). The trigger factor in 8 patients was a tooth extraction and unknown in 3 patients. Clinical examination revealed non-healed extraction sockets in the mandibula of 6 patients and in maxilla of 2 patients. Three patients were present with pain along the mandibular nerve region and swelling of the mouth floor and in four patients palpation revealed exposed bone with irregular bone depositions. The histology of specimens showed osteonecrosis with actinomyces infection in all patients.

All patients underwent unenhanced CT and gadolinium-enhanced MRI of the jaw. CT imaging was performed in a 16-section CT machine (Somatom 16, Siemens Medical Systems, Erlangen, Germany; 45 eff. mAs, 120 kV). The CT images were reconstructed with a section thickness of 1 mm (0.6 mm increment) and multiplanar dental reconstructions were generated using commercially available dental dedicated CT software, respectively. The MRI images (3T unit; Magnetom Trio, Siemens Medical Systems) included unenhanced axial T1-weighted imaging [repetition time (TR) 470 ms, echo time (TE) 11 ms], and T2-weighted imaging (TR 6000 ms, TE 91 ms), as well as axial short-tau inversion recovery (STIR)-weighted imaging (TR 5000 ms, TE 32 ms). After an injection of contrast medium (gadolinium; Magnevist, Schering, Berlin, Germany; 0.2 mmol/kg), using a power injector, fat-saturated axial T1-weighted images (TR 612 ms, TE 11 ms) were acquired.

Two radiologists reviewed all imaging studies in consensus. In MRI studies we assessed the signal intensity change of bony structures, pathological gadolinium enhancement and soft tissue involvement. CT studies were reviewed for the presence of

TABLE 2. Findings in contrast-enhanced imaging of the jaws of 11 patients with bisphosphonate-induced osteonecrosis of the jaws

Findings in contrast-enhanced MRI imaging	Number of patients
Intensity changes of the cortical and subcortical bone structures	11
Contrast enhancement in necrotic bone area	11
Soft-tissue involvement	11
Cervical lymphadenopathy	11

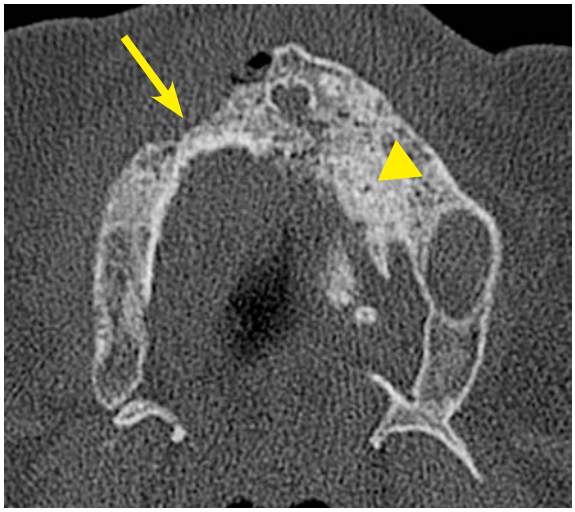
osteolytic and sclerotic changes of the jaw, cortical bony destruction, periostal bone proliferation and involment of inferior alveolar canal.

Results

The degree of bone involvement on CT scan (Table 1) showed osteolytic and sclerotic lesions with cortical bone destruction in all patients, followed by periostal bone proliferation in 7 patients. The sclerotic change encroached on the mandibular (inferior alveolar) canal in 4 patients and 1 patient had sequestration of mandibula. On gadolinium- enhanced MRI of the jaw (Table 2) the intensity changes of the cortical and subcortical bone structures in all patients were recorded (Figures 1 and 2). The osteonecrosis was identified as delimited focal lesions with reduction of the signal on T1- weighted imaging and T2- weighted imaging. In the regions of the open wound low T1-weighted signal correlated with high T2-weighted signal. However in the regions without open wound there was no bright signal from the lesion on the T2-wighted images and enhancement after the administration of paramagnetic contrast material was significantly lower compared to the lesions with bright T2-weighted signal. All the patients had soft-tissue involvement with enhancement in orbicular, buccinator muscle of the mouth or masticator space and adenopathy in submandibular and jugular digastric chain. Maxillary sinus lesions were recorded in 2 patients.

Discussion

Bisphosphonate-associated osteonecrosis is a new disease that is becoming increasingly more common.[1] The adverse effect of bisphosphonat drugs was first described in 2003 by Marx[7], Migliorati[8]



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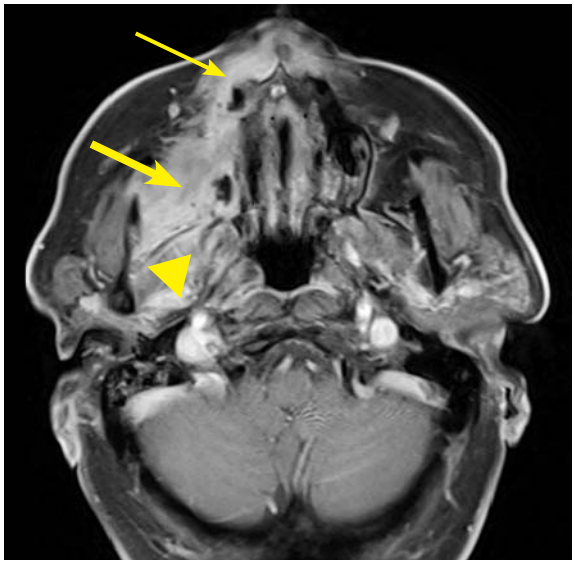

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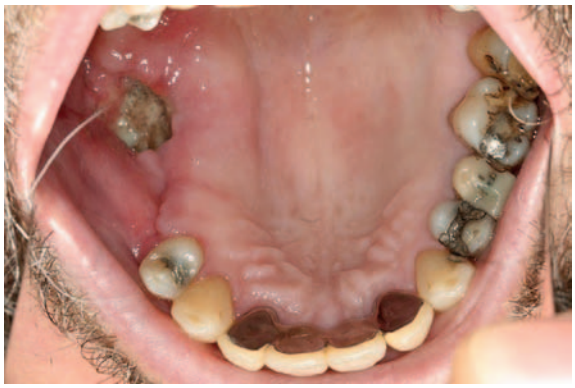

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FIGURE 2. CT and MRI image of a 78-year-old man with multiple myeloma. (A) Axial CT image reveals osteolytic region in the right maxilla (arrow). There is periostal bone reaction, as well as a sclerosis of the maxilla bone marrow on the left side (arrowhead). (B) The corresponding axial T1-weighted, fat-saturated, contrast-enhanced, MRI image demonstrates enhancement in pterygoid and masseter regions (thick arrow). There is also enhancement of necrotic region in right maxilla (thin arrow) and right mandibular ramus with medial cortex resorbtion and periostal reaction (arrowhead). (C) Exposed infected (Actinomyces) bone in the same patient.

and Pogrel[9]; however, connection of phosphorus with osteonecrosis was first established in the 19th century in workers of the matchmaking industry.[10,11]Bisphosphonats are structurally analogous to inorganic pyrophosphates with tropism for solid calcium phosphate. Resistant to enzymatic degradation, they accumulate in bone tissue at high concentrations for long periods of time. Their mechanism of action is based on their ability to inhibit bone resorption: they increase osteoclast apoptosis while inhibiting osteocyte and osteoblast apoptosis. The addition of an amine radical increases the potency of bisphosfonat drugs. It is only with the availability of newer generation bisphosphonat drugs, the aminobisphosphonates (alendronate, ibandronate, risedronate, pamidronate, zoledronate), that side effects like osteonecrosis of the jaw have been described.[12,13] The underlying pathophysiology of bosphosphonats osteonecrosis remains incompletely understood.[10] Bisphosphonates inhibit endothelial proliferation, interrupt intraosseous circulation and bone blood flow, contributing to the development of osteonecrosis.[14] It remains unclear whether patients receiving intravenous bisphosphonates are at a greater risk than those receiving oral bisphosphonates.[1,10,15] Similarly, it remains unclear whether there is a predilection for the jaws. In the literature, mandibular involvement occurs in 59% of cases, maxillary involvement in 27% of cases, and combined mandibular and maxillary involvement in 8% of cases.[16] It seems that bones exposed to constant trauma (like invasive dental procedures in the jaws) have impaired healing that may result in necrosis.[17] Acute exacerbations of bone and soft-tissue infections are the hallmarks of osteonecrosis.[1,10,18] While spontaneous osteonecrosis of the jaw may occur, a triggering event such as dental extraction or surgery is reported in 61.5% of cases.[13,19]

The American Association of Oral and Maxillofacial Surgeons has indicated that for the clinical diagnosis to be made, patients need to exhibit the following 3 criteria: *1)* current or previous treatment with a bisphosphonate; *2)* exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and *3)* no history of radiotherapy.[20] Although the radiographic findings are not a part of the diagnostic criteria, they provide valuable information to the clinician with regard to the course, magnitude, and progression of the disease.[16,20] The radiologic findings of bisphosphonate-associated osteonecrosis of the jaw are not specific and are found in other conditions such as osteomyelitis, osteoradionecrosis and cancer metastasis.[1,12,21] CT is very useful for the ability to see and characterize the extension of the lesions and in detecting cortical involvement while MRI should be reserved for those patients who have soft tissue extension of the disease[6], as the alteration of soft tissue is more detectable with MRI.[22]

Cross-sectional CT imaging of 11 patients from our study with initial and advanced diverse symptoms produced a range of findings, where cortical disruption with mixed lyses and sclerosis of the involved bone were the predominant imaging features. Periostal new bone formation and sequestration was recorded in the patients with advanced stage of the disease. CT finding in our study are consistent with findings in the other reports of the disease.[6,14,23,224] In all our patients we detected lesions with no clinical correlation including focal sclerosis with disorganized trabeculae and difficult cortico-medullary differentiation on CT and low signal on T1 and T2 –weighted MRI images. We believe that these focal lesions are affected areas of the jaw on which a factor (*i.e.* tooth extraction) triggering the process of infection and opening up the focal lesion has not acted. This concurs with another study conducted on fourteen patients with bisphosphonate-induced osteonecrosis.[1]

In MRI the osteonecrosis appeared hypointense on T1-weighted images, but the signal intensity on T2-weighted sequence and after gadolinium enhancement varied. The lesions with intermediate signal on T2-weighted sequence showed very little contrast enhancement, which was suggestive of nonviable bone and the enhancement was probably due to inflammatory reaction caused by Actinomyces infection.[25] Actinomyces infection was present in all specimens of our patient's population. Same observations have been described in study of Bisdas *et al.*[10] and Hansen *et al.*[26] The infection was causing cervical lymphadenopathy in all patients. In patients with necrosis of mandibula pathological enhancement after contrast agent included muscles of the mouth floor, buccinator muscle and orbicular muscle, enhancement of masseter and pterygoid muscle was present in patients with maxilla and mandibular ramus necrosis. Similar MRI findings can be observed in metastatic disease, thus colleration with osseous changes on CT, clinical history and previous therapy is important for correct interpretation of MRI findings.

In conclusion, bisphosphonate related osteonecrosis of the jaw is a well described clinical condition with consistent radiographic findings; however they are not specific for this disease. It is important for radiologist to recognize this entity,

because imaging could be used for early detection in patients susceptible to this disease, which means better prognosis due to early treatment, avoiding biopsy and less necessity of surgery.

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research article

MRI in evaluation of perianal fistulae

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Background. Fistula is considered to be any abnormal passage which connects two epithelial surfaces. Parks' fistulae classification demonstrates the biggest practical significance and divides fistulae into: intersphincteric, transsphincteric, suprasphincteric and extrasphincteric. Etiology of perianal fistulae is most commonly linked with the inflammation of anal glands in Crohn's disease, tuberculosis, pelvic infections, pelvic malignant tumours, and with the radiotherapy. Diagnostic method options are: RTG fistulography, CT fistulography and magnetic resonance imaging (MRI) of pelvic organs.

Patients and methods. We have included 24 patients with perirectal fistulae in the prospective study. X-rays fistulography, CT fistulography, and then MRI of the pelvic cavity have been performed on all patients. Accuracy of each procedure in regards to the patients and the etiologic cause have been statistically determined.

Results. 29.16% of transphincteric fistulae have been found, followed by 25% of intersphincteric, 25% of recto-vaginal, 12.5% of extrasphincteric, and 8.33% of suprasphincteric. Abscess collections have been found in 16.6% patients. The most frequent etiologic cause of perianal fistulae was Crohn's disease in 37.5%, where the accuracy of classification of MRI was 100%, CT was 11% and X-rays 0%. Ulcerous colitis was the second cause, with 20.9% where the accuracy of MRI was 100%, while CT was 80% and X-rays was 0%. All other etiologic causes of fistulae were found in 41.6% patients.

Conclusions. MRI is a reliable diagnostic modality in the classification of perirectal fistulae and can be an excellent diagnostic guide for successful surgical interventions with the aim to reduce the number of recurrences. Its advantage is that fistulae and abscess are visible without the need to apply any contrast medium.

Key words: perianal fistulae; X-rays; CT; MRI; fistulography; abscess

Introduction

As per definition, a fistula is any abnormal passage connecting two epithelial surfaces. Anal fistulae have been known ever since the times of Hypocrates and have been described through centuries. In 1835, Frederick Salmon performed a successful operation in London on the writer Charles Dickens. Goodsall describes the fistulous passage in details, and Parks' classification shows the most practical significance until nowadays. The classification refers to classifying fistulae on: intersphincteric, transsphincteric, suprasphincteric and extrasphincteric. In the more detail anatomical classification, the position of fistulae is used ("clockwise") in respect to the clock hands to avoid any misinterpretation. Complex anal fistulae are those which are followed by risk factors: affected external sphincter anal muscle, forward location in women, multiple passages, incontinence, recurrences of fistulae, local radiation, chronic diarrhoea, Crohn's disease.[1]

Aetiology of perianal fistulae is most commonly associated with the inflammation of anal glands in the Crohn's disease, tuberculosis, pelvic infections, pelvic malignant tumours and with radiotherapy. Idiopathic fistulae are rare and are generally explained by chronic intramuscular anal infection (cryptoglandular hypothesis). In about 70% cases fistulous system drains through skin. Males are affected twice more than females, in ratio 2:1.[2]

Scope of the study

The scope of the study is to indicate a possibility of pre-operative diagnostics with magnetic resonance

TABLE 1. Fistulae classification and the etiology

Patient	age	sex	etiology	Type of fistulae	RTG	CT	MRI	Absces
1	34	M	Crohn's disease	**Intersphincteric**			+	
2	25	M	Crohn's disease	**Transsphincteric**			+	
3	38	M	Crohn's disease	**Transsphincteric**			+	
4	56	F	Ca cerv-radiation	**Transsphincteric**			+	
5	33	M	Crohn's disease	**Transsphincteric**			+	
6	67	F	Crohn's disease	**Intersphincteric**			+	
7	28	M	Crohn's disease	**Transsphincteric**			+	
8	33	M	Crohn's disease	**Transsphincteric**			+	
9	25	F	Unknown	**Intersphincteric**			+	
10	44	M	Unknown	**Suprassphincteric**		+	+	+
11	56	F	Crohn's disease	**Suprassphincteric**		+	+	+
12	56	F	Postpartum	**Rectovaginal**	+	+		
13	45	F	Ca recti	**Rectovaginal**	+	+		
14	31	M	Ulcerous colitis	**Intersphincteric**			+	
15	19	M	Ulcerous colitis	**Extrasphincteric**	+	+	+	
16	55	F	Ca recti-radiation	**Rectovaginal**	+	+	+	
17	45	F	Infla.dermoid cysts	**Rectovaginal**	+	+	+	+
18	30	F	Postpartum	**Rectovaginal**	+	+		
19	34	F	Ulcerous colitis	**Extrasphincteric**	+	+	+	+
20	44	F	Ulcercous colitis	**Transsphincteric**		+	+	
21	42	M	Ulcerous colitis	**Extrasphincteric**	+	+	+	
22	54	M	Ca recti	**Intersphincteric**			+	
23	41	M	Crohn's disease	**Intersphincteric**			+	
24	60	F	Ca recti	**Rectovaginal**	+	+		
Accuracy					**9** 37,5%	**12** 50%	20 83%	4 16,6%

imaging (MRI) in viewing and classifying perianal fistulae, with the aim to have as successful surgical treatment as possible, without recurrences. From the practical surgical point of view, it is of crucial importance to avoid incontinence as a post-operative complication.

Patients and methods

From the 2008 to 2009 we included in the prospective study 24 patients with existing perirectal fistulae. The average age of patients was 41.45 ± 2.6 years, ranging from 19 to 67 years, with the same number of females 50% (n = 12) and males 50% (n = 12).

X-rays fistulography was performed first on all patients, followed by CT fistulography, and then by MRI of the pelvis. X-rays fistulography was performed on X-ray diascope (Practix 100, Philips, Aidhoven, the Netherlands), and after the application of Ultravist contrast medium through perianal fistulous openings. Immediately after that procedure, while the fistulous system was filled with the same contrast medium, the pelvic CT was performed on MDCT (Volume zoom, Siemens, Erlangen, Germany). The MRI pelvic examination was performed on 1.5 T machine (Avanto, Siemens, Erlagen, Germany) by using a routine protocol for pelvic examinations containing T1 3-plane views (axial, coronal and saggital planes), T2 axial and saggital planes, as well as bi-plane (axial and saggital planes) without the application of a contrast medium.

Based on the data obtained, a comparison of all findings has been done, using each particular method.

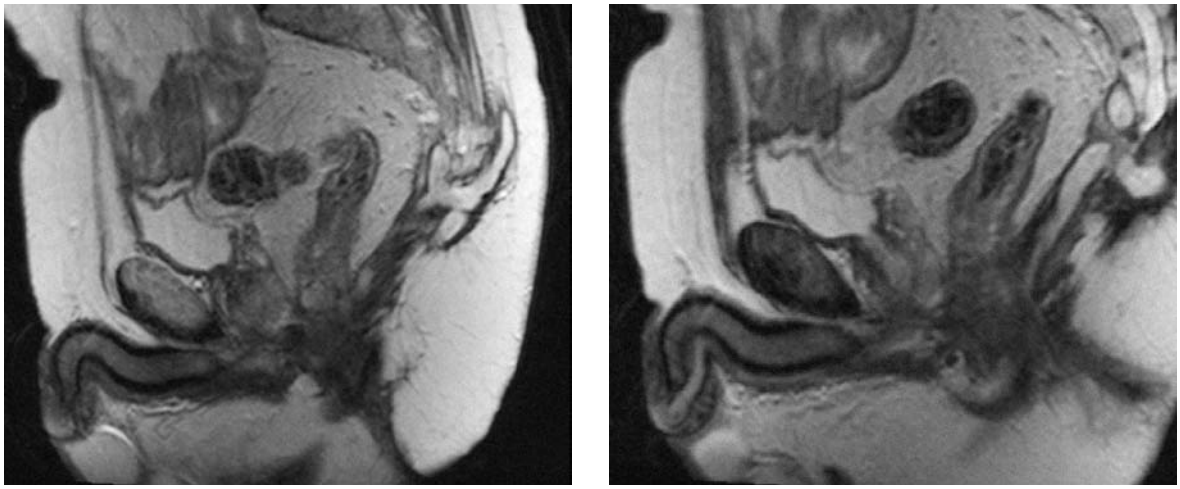

FIGURE 1. Suprasphincteric fistula with the abscess collection in the gluteal region (T2W, sagital).

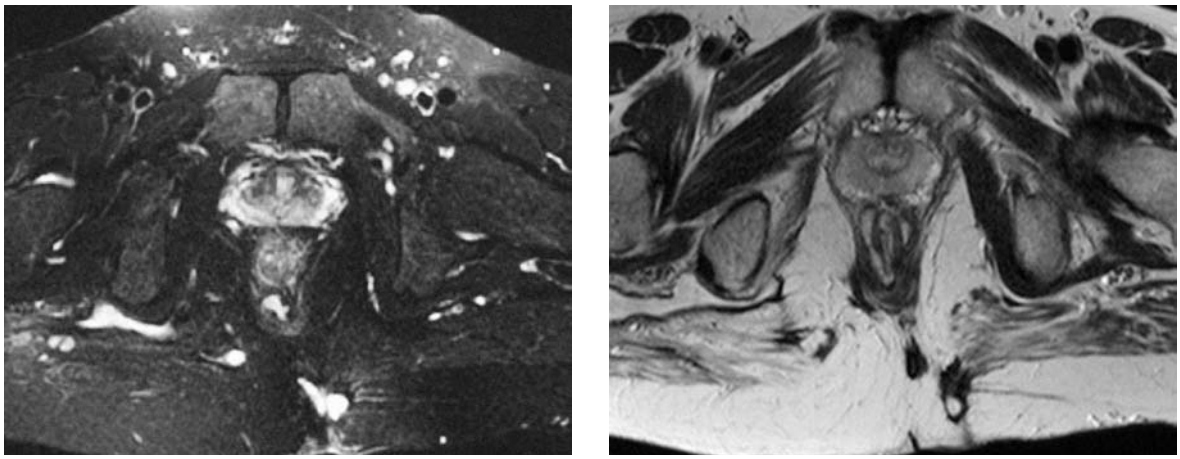

FIGURE 2. Intersphincteric fistula in the shape of a horseshoe with the opening to the left posterior (T2 Fs and T2W tra).

Results

The following has been classified in 24 patients: transsphincteric fistulae in 29.16% of patients (n = 7), intersphincteric in 25% (n = 6), rectovaginal in 25% (n = 6), extrasphincteric in 12.5% (n=3) and suprasphincteric in 8.33% of patients (n = 2). Abscess collections were found in 16.6% of patients (n = 4) (Table 1).

Only 9 fistulae were identified by X-rays fistulography; 12 fistulae were identified by CT fistulography; and 20 by MRI (Table 1). For identifying fistulous ration in respect to the sphincter complex, MRI was a superior method, while for rectovaginal fistulae, CT and X-rays fistulography were better.

The most frequent cause of fistulae in our sample was Crohn's disease with 37.5% (n = 9), followed by ulcerous collitis with 20.9% (n = 5), rectal cancer 16.7% (n = 4), postpartum 8.3% (n = 2), unknown aetiology 8.3% (n = 2), cervical cancer 4.2% (n = 1), and inflammatory dermoid cysts 4.2 % (n = 1) (Table 1).

X-rays fistulography demonstrated the accuracy of 37.5%. (χ^2 = 4.444, p = 0.035), CT fistulography had accuracy of 50%, (χ2 = 6.000, p = 0.014), and the MRI demonstrated accuracy of 83.3%. (χ^2 = 4.800, p = 0.028) (Table 2).

The comparison of results in respect to the sex of the patients demonstrated that there were differences in accuracy in favour of female patients (Table 2). Twenty-six % of all fistulae in our study are rectovaginal, where the total accuracy in females is on increase. The accuracy of X-rays fistulography in females was 75% vs. males 25%. The MRI accuracy for females was 66% vs. males 33%. Slightly higher accuracy for females was demonstrated in CT fistulography, in respect to the MRI,

TABLE 2. Accuracy of all three procedures

			X-rays			CT			MRI		
			Sex		Total	Sex		Total	Sex		Total
			M	F		M	F		M	F	
X-rays	Neg. (-)	Number	10	5	15	9	3	12	0	4	4
		%	83.3	41.7	62.5	75.0	25.0	50.0	0.0	33.3	16.7
	Pos. (+)	Number	2	7	9	3	9	12	12	8	20
		%	16.7	58.3	37.5	25,0	75,0	50.0	100,0	66,7	83.3
Total		Number	12	12	24	12	12	24	12	12	24
		%	50.0	50.0	100.0	50.0	50.0	100.0	50.0	50.0	100.0
			χ^2=4.444	p=0.035		χ^2=6.000	p=0.014		χ^2=4.800	p=0.028	

TABLE 3. The accuracy of procedures varies depending on the aetiology – X-rays

			X-rays							
			Aetiology							Total
			Cervical cancer	Rectal cancer	Inflammatory dermoid cysts	Crohn's disease	Unknown	Postpartum	Ulcerous colitis	
	Neg. (-)	Number	1	1	0	9	2	0	2	15
		%	100.0	25.0	0.0	100.0	100.0	0.0	40.0	62.5
	Pos. (+)	Number	0	3	1	0	0	2	3	9
		%	0.0	75.0	100.0	0.0	0.0	100.0	60.0	37.5
Total		Number	1	4	1	9	2	2	5	24
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
			χ^2=17.600	p=0.014						

because it identified more rectovaginal fistulae compared to the MRI. The lowest accuracy was found in X-rays fistulography.

The accuracy of procedures varies depending on the aetiology as well. X-rays fistulography demonstrates the accuracy in identifying: ulcerous colitis 60%, Crohn's disease 0%, rectal cancer 75%, cervical cancer 0%, inflammatory dermoid cysts 100%, postpartum 100% and of unknown aetiology 0% (Table 3.). CT fistulography demonstrates the accuracy in identifying: ulcerous colitis 80%, Crohn's disease 11.1%, rectal cancer 75%, cervical cancer 0%, inflammatory dermoid cyst 100%, postpartum 100% , and of unknown aetiology 50% (Table 4.). MRI demonstrates the accuracy in identifying: ulcerous colitis 100%, Crohn's disease 100%, rectal cancer 50%, cervical cancer 100%, inflammatory dermoid cyst 100%, postpartum 0%, and of unknown aetiology 100% (Table 5.) (Figures 1, 2, 3).

Discussion

Not so long time ago, surgeons performed operations on perirectal fistulae without the previous radiological assessment. The surgical examination under anaesthetics (EUA) consisted of visual inspection, palpation with the probe of a fistulous passage under general anaesthesia. Numerous diagnostic modalities failed in visualisation and classification of perianal fistulae.

Fistulography, as the earliest X-rays method, cannot classify fistulae due to the inadequate

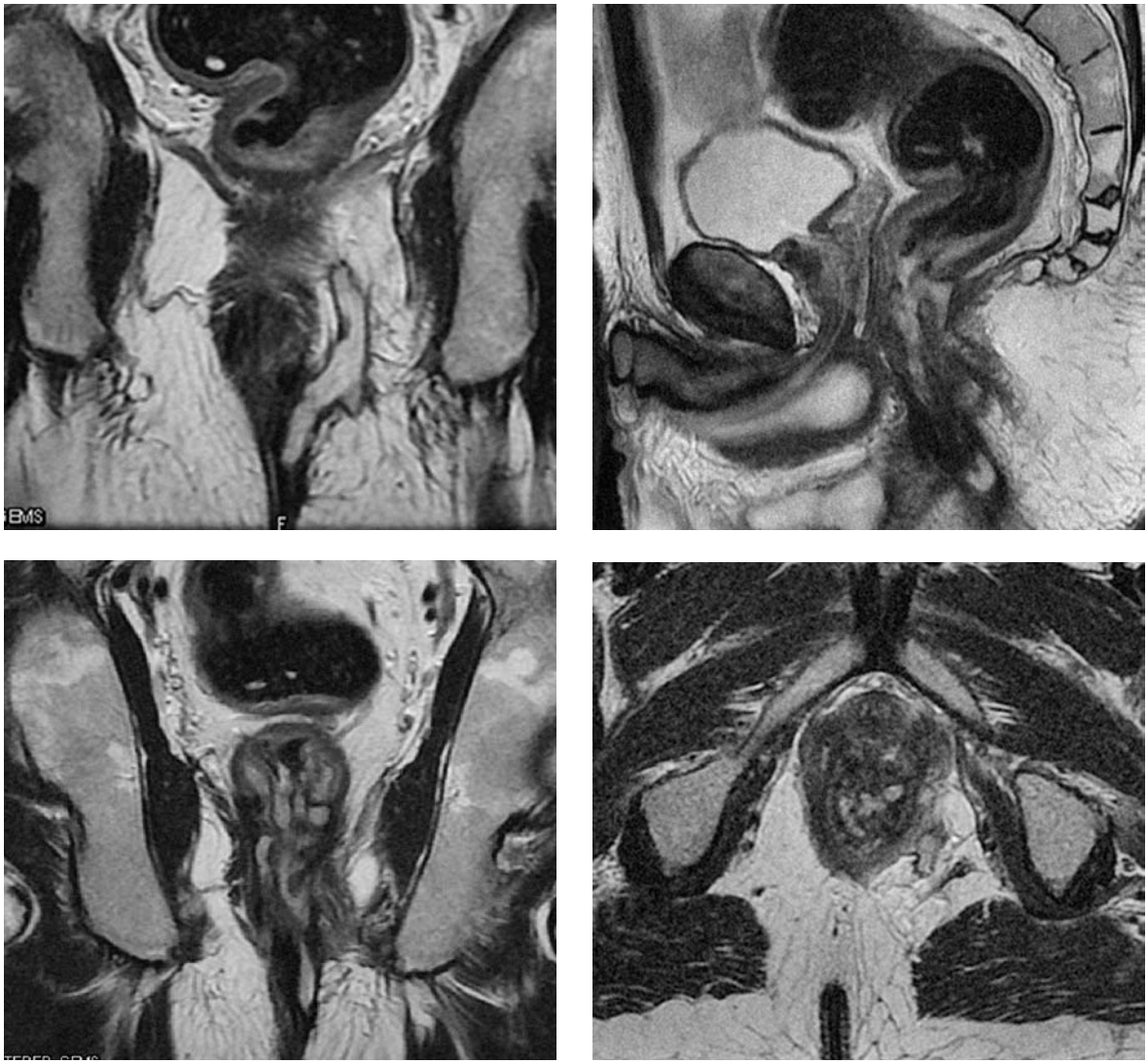

FIGURE 3. A complex transsphincteric fistula to the left (T2W cor,T2W sag,T2W tra).

showing of anatomic structures, so that frequently it is unclear and difficult for the interpretation. CT can identify the existence of fistulous passages, either through non-ionic water solluble contrast media being inserted per rectum or through the fistulous opening. However, it is not sufficiend for a more detailed analysis of the whole complex of primary and numerous secondary branches in the fistulous system. Although the application of multidetector CT fistulography with the option of isotropic voxels and multiplaned imaging can bridge the aforementioned issues, researchers do not show enough interest in this field. It is obvious that the superiority of MRI and endorectal ultrasound (EUS) examination in the evaluation of perirectal fistulae provides a better motivation to the researchers.[3]

MRI with the superficial body-coil, besides other anatomic structures in the pelvis, shows excellent results in showing rectum, perianal region, internal, external anal sphincter, levator ani, ishiorectal and ishioanal region.[4] In the evaluation of perirectal fistulae, it is very important to describe the relationship between fistula and the sphincteric mechanism in the coronal plane (Figure 3). It is equally important to describe the primary fistulous passage as well as the secondary ramification and possible associated abscess due to axial images. Images in the saggital plane are suitable for showing rectovaginal fistulae and the pre-sacral region. The surgical exploration without previous MRI diagnostics can be made difficult due to the presence of fibrosis and oedema, so that the MRI can identify the hidden intersphincteric space with the cap-

TABLE 4. The accuracy of procedures varies depending on the aetiology – CT

CT									
			Aetiology						Total
			Cervical cancer	Rectal cancer	Inflammatory dermoid cysts	Crohn's disease	Unknown	Postpartum	Ulcerous colitis	
	Neg. (-)	Number	1	1	0	8	1	0	1	12
		%	100.0	25.0	0.0	88.9	50.0	0.0	20.0	50.0
	Pos. (+)	Number	0	3	1	1	1	2	4	12
		%	0.0	75.0	100.0	11.1	50.0	100.0	80.0	50.0
Total		Number	1	4	1	9	2	2	5	24
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
			χ^2=14.444	p=0.087						

TABLE 5. The accuracy of procedures varies depending on the aetiology – MRI

MR									
			Aetiology						Total
			Cervical cancer	Rectal cancer	Inflammatory dermoid cysts	Crohn's disease	Unknown	Postpartum	Ulcerous colitis	
	Neg. (-)	Number	0	2	0	0	0	2	0	4
		%	0.0	50.0	0.0	0.0	0.0	100.0	0.0	16.7
	Pos. (+)	Number	1	2	1	9	2	0	5	20
		%	100.0	50.0	100.0	100.0	100.0	0.0	100.0	83.3
Total		Number	1	4	1	9	2	2	5	24
		%	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0
			χ^2=16.800	p=0.019						

tured puss without rupturing the cutaneous layer. It is also useful in high fistulae – both transsphincteric and extrasphincteric. Fistulous passage, abscess, as well as all inflamed structures, show on T2W sequences high signal intensity, so they are easily noticed in respect to the muscles which have low signal intensity. On non-contrasted T1W sequences, fistulous passages (especially the secondary ones, the smaller ones), as well as abscess collections are identified with difficulties due to the moderate signal intensity of normal structures of the sphincter muscle and levatore ani. Therefore, it is recommended to use sequences with suppressed fats as the i.v. application of Gadolinium as a contrast medium. The fistulous opening on skin can be filled with Gadolinium, thus obtaining the picture of fistulous system in hipersignal in T1W time, or by a cheaper method – by injecting physiological solution with showing the fistulous system in hipersignal in T2W time.

There is not a large number of published studies in relation to the fistulography. Thus, Kuipers and Schulpen as far as in 1985 emphasized that fistulography is a reliable and accurate method in

only 16% cases.[5] The best results were obtained by Weisman *et al.* who managed to obtain reliable fistulography in half of the examined cases – 27 patients in his study, which generally represents only very modest results.[6]

The first reporting on the accuracy of MRI in detection and classification of perianal fistulae was from 1992 – 1994 in Lunnis' publications, with the matching of 86-88% between MRI and surgical findings.[7,8] EUS is not a comfortable procedure, however, it has a very good spatial resolution due to the close contact of the probe (10MHZ) with the rectal wall, which gives it the superiority in evaluation of fistulous openings within the rectum and the level of disruption of the sphincter in post-surgically incontinent patients. MRI is more comfortable[4] and better shows intersphincteric abscesses. Halligan and Stoker claim that MRI assists the surgeon to reduce post-surgical recurrences for 75%, and that the EUS is only an alternative when it is not possible to perform the MRI.[9] Hussain *et al.* from the Netherlands, in his study from 1996, talked about the superiority of MRI in classification of fistulae compared to the EUS (89 vs 61%).[10] Spenser's study from 1996, in which body-coil was used, demonstrated the accuracy of the MRI in showing perirectal fistulae of 88%.[11] The same author, two years later, in 1988, obtained the classification of fistulae by EUS of 81%, and by the MRI of 90%.[12] Sensitivity of the primary fistulous passage reaches up to 100%, however, with the specificity of 86%. Yee *et al.* concludes in his study that the native endoscopic ultrasound does not detect rectovaginal fistulae.[13]

In the recent times, ultrasound visibility of fistulae filled with peroxide has been researched, which is strictly recommended for the pre-surgical evaluation in patients with recurrences of fistulae. Gustafson *et al.* claimed that the endoscopic EUS complemented the MRI in classification of fistulae.[14]

The optimal diagnostic approach is a combination of EUS, examination under anaesthesia (EUA) and MRI in patients with fistulae who have the Crohn's disease, reports Schwartz *et al.* in his article.[15] The Viennese group of radiologists, in their study, obtains the accuracy in classification of fistulae by the MRI of 84%, vs EUS of 60%.[16]

Gravante and Giordano in 2008 promoted 3D EUS as equal to the MRI in the examination of fistulae. The accuracy of the MRI was obtained in the range of 90 % compared with the EUS which obtained 81%.[17] Schratter-Sehn *et al.* obtained higher sensitivity by the EUS of 82% compared to n CT of 24% in the classification of perianal fistulae in the Crohn's disease, while Schaefer *et al.* obtains the matching with the surgical findings of 89%.[18,19] In our study, we obtained the accuracy in classification of fistulae by X-rays of 37.5%, with the CT accuracy was 50%, and the MRI accuracy was 83%. The most frequent aetiological cause of perianal fistulae was Crohn's disease of 37.5%, where the accuracy of classification by the MRI was 100%, by CT of 11% and by X-rays was 0%. Ulcerous colitis was on the second place with 20.9%, where the accuracy in that respect was 100% by the MRI, 80% by CT and 0% by X-rays. All other etiological causes of fistulae including radiation, which is a serious side effect after oncological treatment[20,21], were 41.6%. Abscess collection was found in 16.6 patients.

Conclusions

MRI is a reliable diagnostic modality in the classification of perirectal fistulae and can be an excellent diagnostic guide for successful surgical interventions with the aim to reduce the number of recurrences. Its advantage is that fistulae and abscess are visible without the need to apply any contrast medium.

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case report

Mammographycally occult high grade ductal carcinoma *in situ* (DCIS) as second primary breast cancer, detected with MRI: a case report

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Background. Contralateral breast cancer (CLB) is the most common second primary breast cancer in patients diagnosed with breast cancer. The majority of patients harbouring CLB tumours develop the invasive disease. Almost all invasive carcinomas are believed to begin as ductal carcinoma in situ (DCIS) lesions. The sensitivity of MRI for DCIS is much higher than that of mammography.

Case report. We report the case of a woman who was treated with breast conserving therapy 10 years ago. At that time the invasive medullary carcinoma was diagnosed in the left breast. Ten years later mammographically occult DCIS was diagnosed with MRI-guided core biopsy in contralateral breast.

Conclusions. There might be a potential role of MRI screening as part of an annual follow-up for patients diagnosed with breast cancer.

Key words: high-grade DCIS; second primary breast cancer; MRI

Introduction

Contralateral breast cancer (CLB) is the most common second primary breast cancer in patients diagnosed with breast cancer.[1] The annual risk of developing any CLB remains constant at approximately 0.75% and persists for at least 20 years after the treatment. The majority of patients (83%) harbouring CLB tumours develop the invasive disease.[2] There is little data on the use of MRI as a screening tool to detect a recurrence after the breast-conserving therapy. Gorechland *et al.* concluded that MRI screening would not have been cost-effective and was unlikely to have improved the overall survival.[3] However, the role of MRI in detection of invasive carcinoma had already been known, Kuhl *et al.* published in 2007 that MRI is more sensitive for detecting ductal carcinoma *in situ* (DCIS) than mammography (92% vs. 56%), especially for high-grade DCIS without necrosis (92% vs. 35%).[4] Almost all invasive carcinomas are believed to begin as DCIS lesions.[5] Therefore, some invasive carcinomas can be prevented by a timely intervention on the basis of MRI findings.

Case report

A 47-year-old female patient was treated by breast conserving surgery in 1999. At that time invasive medullary carcinoma was diagnosed in her left breast. The dissection of axilla has been done and there was no metastatic lymph node. She received adjuvant chemotherapy and a radiation therapy. She had the regular clinical and mammographic follow-up. In April 2009 her last mammography was obtained (Figure 1). Radiological findings were evaluated according to the Breast Imaging

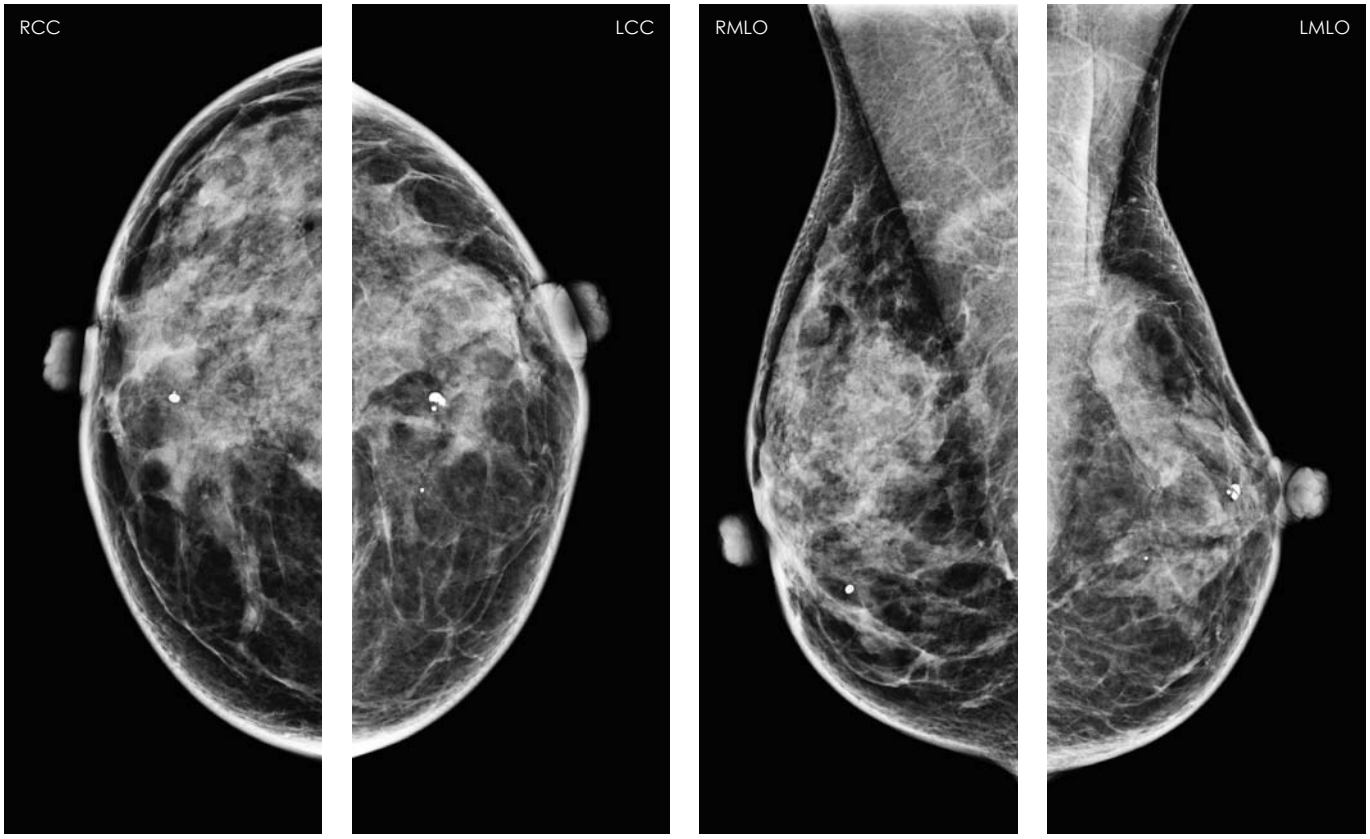

FIGURE 1. The mammograms were categorized as BI-RADS 2 (cyst, benign calcifications, postoperative changes). The breast density was categorized as ACR III. There was no change in comparison with previous mammograms.

Reporting and Data System by American College of Radiology (Figure 1).

In November 2009, she visited her doctor earlier because of changes in her right nipple. The nipple became retracted. She also had pain in her breast. Breast MRI was performed, using a 1.5-T magnet with a dedicated bilateral breast surface coil with prone position. The imaging protocol and parameters were as follows: axial T1-weighted image and short-tau inversion recovery (STIR) of both breasts were obtained with 3 mm slice thickness. Next, T1-weighted images were acquired using a 3D fast low angle shot (FLASH) through both breasts. Pre-contrast images were obtained in the axial plane with a slice thickness of 1.0 mm with a distance factor 20% before the administration of the contrast agent. Then, five sequential contrast-enhanced images were acquired at every 1 min 23 s. The MRI findings were categorized according to Breast Imaging Reporting and Data system (BI-RADS) lexicon.

After a gadolinium injection and subtraction a bilateral enhancement was seen: On the left side there was a 7 x 5 mm mass-like enhancement in the scar area. The margins were round and well circumscribed, the enhancement was homogeneous, and kinetic was 173% initial enhancement with plato BI-RADS 2 (Figure 2).

On the right there was a non-masslike enhancement. The enhancement pattern was ductal-linear in distribution measured 8 x 3mm. The internal enhancement was homogenous -BI-RADS 3-4 (Figure 3).

On the precontrast T2-weighted sequence there was a hiperintensive signal in the area of ductal enhancement in the right breast. There were small cysts bilaterally (Figure 4).

The targeted ultrasound was performed, using 5-12 MHz linear transducer (Toshiba Aplio, Nasu, Japan). In the right breast there was no pathology. In the left breast there was a small tumour 5 x 4 mm categorized as BI-RADS 4 (Figure 5). The fine needle US guided biopsy was performed and cytology was inconclusive. During the procedure the patient was very anxious and difficult to communicate with.

Because of the MRI finding in the right breast (mammogaphicaly occult, targeted ultrasound negative) and because of the patient's history the

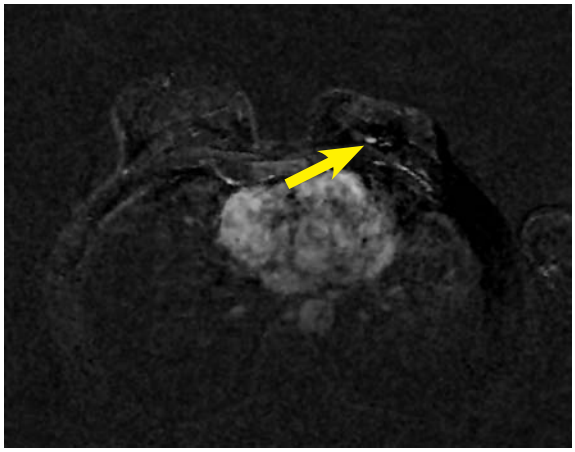

FIGURE 2. Axial T1-weighted image after Gadolinium injection (2nd minute) and subtraction, focal enhancement 7 x 5 mm in the left breast in the prepectoral region (arrowhead).

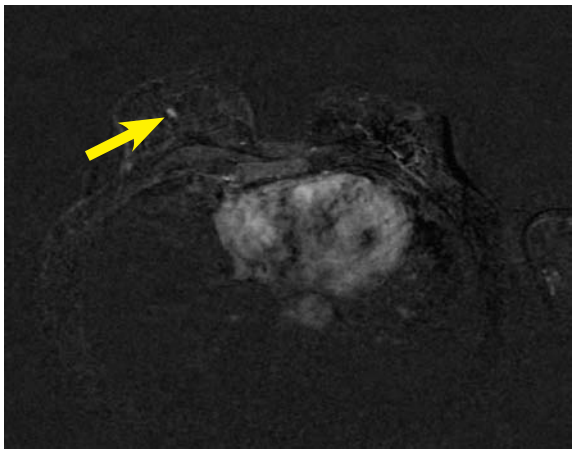

FIGURE 3. Axial T1-weighted image after Gadolinium injection (2nd minute) and subtraction, ductal homogenous enhancement in the right breast 8 x 3 mm (arrowhead).

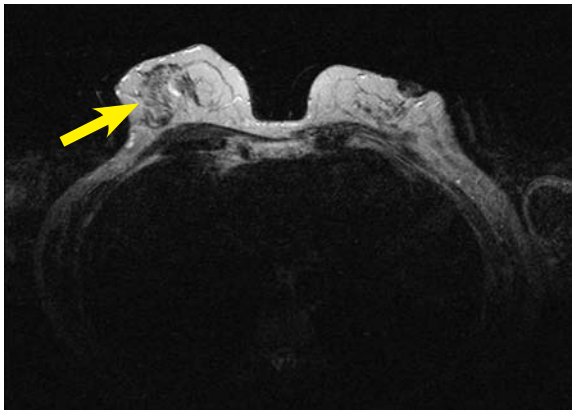

FIGURE 4. Axial T2-weighted image, a hiperintensive signal in the right breast (arrowhead).

MRI-guided core biopsy was performed. MRI-guided vacuum-assisted breast biopsy was performed with MRI-supported Breast Immobilization and Biopsy System with the 4-channel breast coil in prone position. Axial T1- weighted images were acquired using a 3D FLASH through both breasts. Precontrast images were obtained in the axial plane with a slice thickness of 1.0 mm with distance factor 20%. Twenty seconds after contrast agent had been injected, another axial T1-3D FLASH sequence was performed with an injection of 0.1 mmol/kg of body weight of gadopentetate dimeglumine. Biopsy was performed with a 9-gauge MRI compatible vacuum-assisted biopsy. The biopsy site was marked with a titanium clip. "Postclip" axial 3D FLASH was performed to assess clip deployment.

The histological finding was DCIS-high grade, without any calcification. The patient was operated. The breast conserving therapy was performed. The clip in the right breast was localized by the radioguided occult lesion localization (ROLL) method under X-ray guidance. The lesion in her left breast was localized by ROLL method under US guidance. The pathologic results were the remnant foci of high-grade DCIS in the right breast and benign changes in the left breast.

Discussion

The screening MRI has not yet been included in surveillance for patients treated by a breast-conserving therapy. However, the patient visited her doctor earlier because of changes in her right nipple, what demonstrated the importance of the breast-self examination.[6] In addition, in our case MRI was performed because the patient had retracted nipple and dense breast.[3] DCIS was represented as a ductal-linear homogenous enhancement on MRI images. The ductal-linear homogenous enhancement is a type of non-masslike enhancement.[7,8] The path of enhancement follows the galactophoric system. The internal feature of the enhancement was homogenous in our case. DCIS and inflammatory disease are the most common causes for such a type of enhancement. The targeted ultrasound was negative, as we had expected.

Among the non-masslike enhancement detected initially on MRI, only 11% could be retrospectively detected by ultrasound and sonographically occult lesions have 22% probability of malignancy.[9-12] Although the ductal enhancement was small, it measured only 8 x 3 mm, we decided to perform MRI-guided core biopsy and the histological result was conclusive.[13,14] There was also a lesion which

was incidentally found in the scar area of the left breast, which finally proved to be benign.

High-grade DCIS with no calcifications is not easy to diagnose by mammography due to the lack of typical malignant calcifications or masses, especially in dense breasts. Calcifications with or without mass are more common in women under 50 years.[11] Autopsy studies have shown that almost 9% of women have undetected DCIS.[15]

Almost all invasive carcinomas are believed to begin as DCIS lesions but the time course of transition is unknown. Whether all DCIS will ultimately evolve to the invasive disease is unclear.[16,17] In 2007 an article was published, that sensitivity of MRI for high-grade DCIS is much higher than that of mammography (92% vs. 56%), especially for high grade DCIS without necrosis (97% vs. 35%).[4] If we pick up all cases of DCIS we would prevent virtually all cases of breast cancer, including CLB. CLB is the most common second primary breast cancer in patients diagnosed with breast cancer. The annual risk of developing any CLB remains constant at 0.75% per year after the treatment and persists for at least 20 years. The majority of patients (83%) harbouring CLB tumours develop invasive disease.[2] The detection of second breast cancers in the asymptomatic phase leads to the detection of early-stage cancer and it improves the relative survival alike in other cancer's localisations between 27% to 47%.[18,19]

In conclusion, by the Breast MRI Guidelines from the European Society of Breast Imaging[14], currently there is not sufficient evidence to recommend the screening with MRI to patients treated by breast conserving surgery. But we might say that our case, in accordance to the European Guidelines, justifies MRI as a problem-solving modality when: the findings of conventional imaging are inconclusive and it is impossible to image sufficiently the primary tumour region after the conservative therapy with mammography.

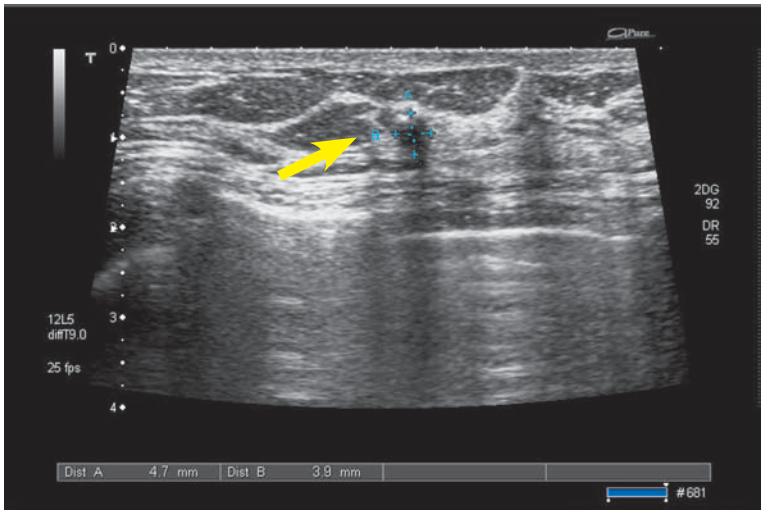

FIGURE 5. Small lesion in the left breast 5 x 4 mm, transonic with unsharp margins, vertically orientated, BI-RADS 4 (arrowhead).

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research article

Effect of response quality and line of treatment with rituximab on overall and disease-free survival of patients with B-cell lymphoma

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Background. The introduction of rituximab into the treatment of patients with non-Hodgkin's lymphomas has improved the overall response rate, as well as the response duration and the overall survival of patients with B-cell lymphomas. But only a few studies have addressed the question whether the better response (complete response) and the early introduction of rituximab into the treatment translate into the better survival. The aim of this retrospective study was to assess the potential relationship between either the quality of the response or the line of the rituximab treatment and the overall survival (OS) as well as the disease-free survival (DFS) of patients with B-cell lymphomas.

Patients and methods. In the study, we analysed treatment outcomes in patients with different histological types of B-cell lymphomas who were treated at the Institute of Oncology between 2003 and 2007 with rituximab and chemotherapy. We included only patients who had the level of CD20 expression assessed prior to the introduction of the treatment with quantitative flow-cytometric measurements. The OS and DFS were evaluated by Kaplan-Meier survival curves.

Results. One hundred and fourteen patients were enrolled in the study. Patients who achieved a complete response after the rituximab containing treatment had a significantly longer OS than those reaching a partial response (hazard ratio [HR], 0.34; 95% CI, 0.05 to 0.91, P = 0.0375) and than patients with stable (hazard ratio [HR], 0.11; 95% CI, 0.0002 to 0.033, P < 0.0001) or progressive disease (hazard ratio [HR], 0.09; 95% CI, 0.003 to 0.03, P < 0.0001). Patients who achieved a complete response (CR; n = 70; 61.4%) had also a significantly longer DFS (hazard ratio [HR], 0.26; 95% CI, 0.021 to 0.538, P = 0.0068) than those reaching only a partial response (PR; n = 17; 14.9%). Patients treated with rituximab as the first-line treatment (n = 50; 43.9%) had a significantly longer OS than those treated with rituximab for the first (hazard ratio [HR], 0.27; 95% CI, 0.106 to 0.645, P = 0.0036) or second relapse (hazard ratio [HR], 0.22; 95% CI, 0.078 to 0.5, P = 0.0006). Also the DFS of patients treated with rituximab as the first-line treatment (n = 46; 52.9%) was significantly longer (hazard ratio [HR], 0.32; 95% CI, 0.088 to 0.9, P = 0.0325) than in patients treated with rituximab for their first relapse (n = 25; 28.7%).

Conclusions. These data indicate that a better response to rituximab therapy presumably translates into an improved OS and DFS for patients with B-cell lymphomas. The early introduction of rituximab into the treatment (i.e. first-line treatment) might improve OS. Therefore, the response adapted first-line therapy with rituximab should be considered when the treatment decision is taken in B-cell lymphoma patients.

Key words: B-cell lymphoma; rituximab; response quality, the line of treatment; overall survival; disease-free survival

Introduction

B-cell lymphomas are a group of diseases characterized by the proliferation of lymphoid tissue and occasionally by the presence of abnormal lymphoid elements in the peripheral blood.[1] The incidence of these malignancies has been increasing over the past several decades by approximately 3% per year.[2] Over the last two decades, there has been a significant increase in management options of these patients, consisting of the observation in case of indolent lymphomas, various chemothera-

pies (alkylating agent-based, fludarabine-based, antracycline-based), hematopoietic stem-cell transplantation and biologic therapies among which also the therapy that targets the CD20 antigen, such as rituximab.

The introduction of rituximab into the treatment of patients with non-Hodgkin lymphoma has improved the overall response rate, as well as the response duration and the overall survival of patients with B-cell lymphomas.[3,4] Although there has been some evidence that in the treatment of lymphoma patients the better response is associated with the prolonged disease-free survival, the correlation between the quality of response and the survival still remains unknown.[4-9] Recently published studies have indicated that a better response to first-line treatment translates into an improved survival for patients with follicular lymphoma and also with other malignomas.[10,11] With our retrospective study we, therefore, wanted to assess the potential correlation between either the quality of response or the line of the rituximab treatment with both the overall survival (OS) and the disease-free survival (DFS) of patients with B-cell lymphomas.

Patients and methods

Patient population

Patients with different histological types of B-cell lymphomas treated with the rituximab containing therapy between 2003 and 2007 at the Institute of Oncology Ljubljana were included in our retrospective study. Because this study was a part of a more extensive research on the correlation between the CD20 expression and treatment outcome just patients who had the level of CD20 expression assessed prior to the introduction of the treatment with quantitative flow-cytometric measurements were selected. These patients represented approximately 33.5% of all patients treated routinely with rituximab in that period.

Patients received treatments according to the then protocol at our Institute. Aggressive lymphomas were predominately treated with the rituximab containing therapy in the first-line and just relapsing patients who had not previously received rituximab were treated in the second or consecutive lines. On the other hand, most patients with indolent lymphomas were in line with the recommendations not treated with the rituximab containing therapy until relapse. Rituximab – chemotherapy combinations were selected according to the histological type of lymphoma, extent of the disease and previous

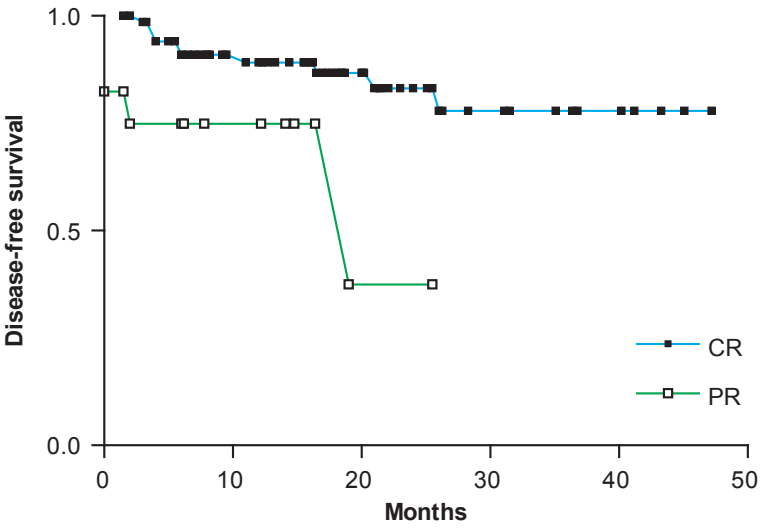

FIGURE 1. Disease-free survival after treatment with rituximab and chemotherapy according to the response quality. *CR* - complete response, *PR* - partial response

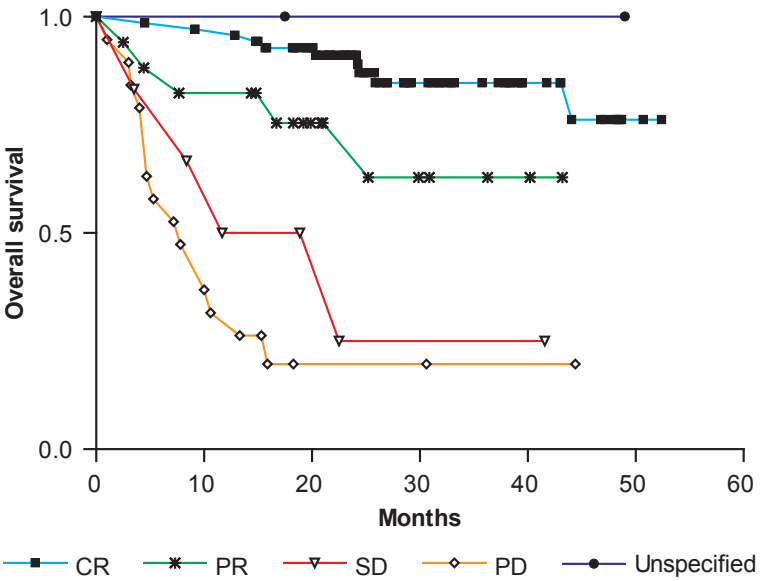

FIGURE 2. Overall survival after treatment with rituximab and chemotherapy according to the response quality. *CR* - complete response, *PR* - partial response, *SD* - stable disease, *PD* - progressive disease, *ORR* - overall response rate, *Unspecified* – response not specified

treatments. Most of the patients received R-CHOP (75.4%). Patients with a more limited disease were planned to receive 6 and patients with extensive disease up to 8 chemo-immunotherapy cycles.

Response to treatment

The treatment response data were retrospectively noted from patients' records for the specified B-cell lymphoma patients. The quality of the response was assessed by Cheson's criteria.[12]

In the next step, the OS data for all included B-cell lymphoma patients together with the

TABLE 1. Patients' characteristics together with the distribution of patients according to the lines of treatment

Patient's characteristics				
Gender	64 males (56.1%); 50 females (43.9%)			
Age	Median 58.5 years (range 19 to 82 years)			
Histological type	Number (%) of patients	Number of patients treated with rituximab as first-line treatment (%)	Number of patients treated with rituximab as second-line treatment (%)	Number of patients treated with rituximab as third or subsequent line of treatment (%)
DLBCL	42 (36.8)	33 (78.6)	8 (19)	1 (2.4)
FL	30 (26.3)	6 (20)	11 (37)	13 (43)
CLL	5 (4.4)	0	2 (40)	3 (60)
MCL	20 (17.5)	8 (40)	6 (30)	6 (30)
MZL	2 (1.8)	0	1 (50)	1 (50)
Unclassified	15 (13.2)	3 (20)	5 (33)	7 (47)
Total	114 (100)	50 (43.9)	33 (28.9)	31 (27.2)

DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, CLL = chronic lymphocytic leukemia, MCL = mantle cell lymphoma, MZL = marginal zone lymphoma, Unclassified = unclassified B-cell lymphoma

TABLE 2. The distribution of patients receiving rituximab according to the response quality

Response quality	Number of patients	% of all patients
CR	70	61.4
PR	17	14.9
SD	6	5.3
PD	19	16.7
Unspecified	2	1.8
ORR	87	76.3
Total	114	100

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ORR = overall response rate, Unspecified = response not specified

DFS data for the B-cell lymphoma patients who achieved the complete (CR) or the partial response (PR) after the treatment were obtained.

The OS was assessed by Kaplan-Meier survival curves from the beginning of the treatment for all patients. The response duration expressed as the DFS was evaluated by Kaplan-Meier survival curves from the end of the treatment for the patients attaining CR or PR after the rituximab containing treatment.

Statistical analysis

The difference between the survival curves was assessed by a log-rank test and the difference between the overall response rates by a hi-square test.

Results

Characteristics of the study participants

One hundred and fourteen patients with different histological types of B-cell lymphomas who were treated with rituximab and chemotherapy between 2003 and 2007 and had the level of CD20 expression assessed prior to the introduction of the treatment with quantitative flow-cytometric measurements were included. There were 64 males and 50 females with the median age of 58.5 years (range 19 to 82 years). The majority of patients had the diffuse large B-cell lymphoma (DLBCL; 42 patients; 36.8%) and follicular lymphoma (FL; 30 patients; 26.3%). Patients' characteristics together with the distribution of patients according to the lines of the treatment are given in Table 1.

In the majority of patients, rituximab was given as the first-line treatment (50 patients; 43.9%), while 33 patients (28.9%) received it as the second-line treatment, and 31 patients (27.2%) as the third or subsequent line of the treatment. There was, however, some difference between aggressive and indolent lymphomas – namely 78.6% of patients with aggressive lymphomas received rituximab as the first-line treatment, 19% as the second-line treatment and 2.4% as the third/subsequent line treatment while just 23.6% of patients with indolent or unclassified lymphomas were treated with rituximab as the first-line, 34.7% as the second-line and 41.7% as the third/subsequent line of the treatment (Table 1).

All patients received at least 3 and up to 8 cycles of the treatment. No patients were excluded due to serious side effects. The follow-up of side effects was by all means not the objective of this study, yet we have to mention that in the routine setting serious side effects of the rituximab treatment have been during a longer period of time observed in less than 1% of patients.

The effect of the response quality on OS and DFS

The overall response rate (ORR) of the treatment with rituximab and chemotherapy regardless of the histological type of lymphoma or of the line of treatment was 76.3% (61.4% CR; 14.9% PR). The distribution of patients receiving rituximab according to the response quality is given in Table 2.

Table 3 additionally gives the distribution of patients receiving rituximab according to the response quality and the type of lymphoma, yet the data are given just for those lymphoma type groups that comprise more than 10 patients.

In continuation, the DFS was evaluated from the end of the treatment for patients achieving CR and PR to the treatment with rituximab and chemotherapy (87 patients; 76.3%) and is according to the response quality presented in Figure 1.

The B-cell lymphoma patients treated with rituximab who achieved a complete response (CR; n = 70; 61.4%) had a significantly longer DFS (hazard ratio [HR], 0.26; 95% CI, 0.021 to 0.538, P = 0.0068) than those reaching just a partial response (PR; n = 17; 14.9%). In patients who achieved CR, the median response duration has not been reached yet, while for the patients who achieved PR, it was 19 months.

The OS was assessed from the beginning of the treatment for all 114 patients treated with rituximab and chemotherapy. Figure 2 presents the OS after the treatment with rituximab and chemotherapy according to the response quality.

The B-cell lymphoma patients who achieved a complete response after the rituximab therapy had a significantly longer OS than those reaching a partial response (hazard ratio [HR], 0.34; 95% CI, 0.05 to 0.91, P = 0.0375), and than patients with stable (hazard ratio [HR], 0.11; 95% CI, 0.0002 to 0.033, P <0.0001) or progressive disease (hazard ratio [HR], 0.09; 95% CI, 0.003 to 0.03, P <0.0001). Patients who achieved a partial response had a significantly longer OS than those with progressive disease (hazard ratio [HR], 0.24; 95% CI, 0.095 to 0.589, P = 0.002). In patients with stable disease after the rituximab therapy, the median OS was 17.1 months, while for the patients with progressive disease, it was only 7.8 months. The median OS has not been reached for patients with CR, PR and unspecified response.

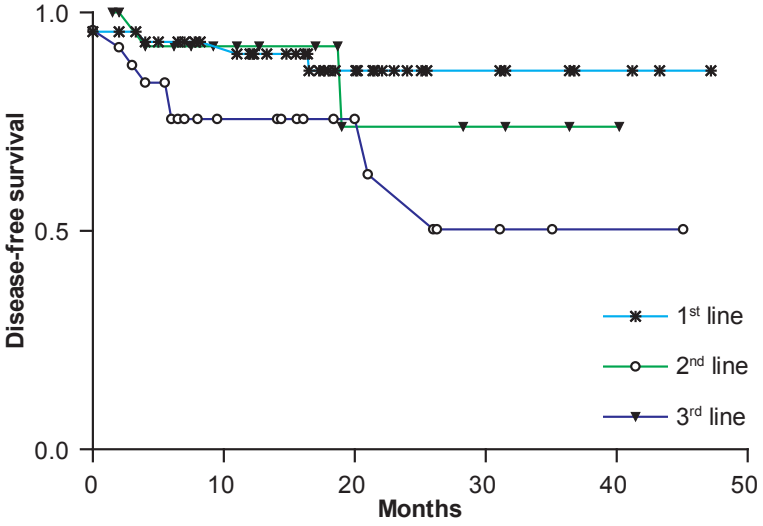

FIGURE 3. Disease-free survival after treatment with rituximab and chemotherapy according to the lines of treatment.

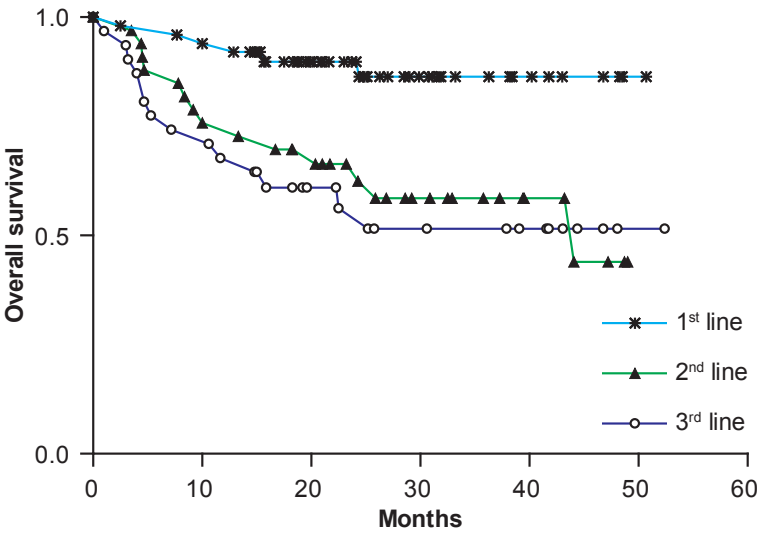

FIGURE 4. Overall survival after treatment with rituximab and chemotherapy according to the lines of treatment.

The effect of the line of the treatment with rituximab on OS and DFS

The distribution of patients receiving rituximab according to the response quality and the line of the treatment is given in Table 4.

The duration of the response expressed as the DFS for those 87 patients (76.3%) achieving CR and PR to the treatment with rituximab and chemotherapy is according to lines of the treatment shown in Figure 3.

TABLE 3. The distribution of patients receiving rituximab according to the response quality and type of lymphoma

Response quality	DLCBL		FL		MCL		Unclassified	
	Number of patients	% of all patients	Number of patients	% of all patients	Number of patients	% of all patients	Number of patients	% of all patients
CR	29	69	22	73,3	9	45	8	53,3
PR	8	19	3	10	2	10	3	20
SD	0	0	1	3,3	4	20	1	6,7
PD	4	9,5	3	10	5	25	3	20
Unspecified	1	2,4	1	3,3	0	0	0	0
ORR	37	88,1	25	83,3	11	55	11	73,3
Total	42	36.8	30	26.3	20	17.5	15	13.2

CR = complete response, *PR* = partial response, *SD* = stable disease, *PD* = progressive disease, *ORR* = overall response rate, *Unspecified* = response not specified, *DLBCL* = diffuse large B-cell lymphoma, *FL* = follicular lymphoma, *MCL* = mantle cell lymphoma, *Unclassified* = unclassified B-cell lymphoma

TABLE 4. The distribution of patients receiving rituximab according to response quality and the line of treatment

Response quality	All lines		1st line		2nd line		3rd line	
	Number of patients	% of all patients	Number of patients	% of all patients	Number of patients	% of all patients	Number of patients	% of all patients
CR	70	61.4	36	72	21	63.6	13	41.9
PR	17	14.9	10	20	4	12.1	3	9.7
SD	6	5.3	1	2	2	6.1	3	9.7
PD	19	16.7	2	4	5	15.2	12	38.7
Unspecified	2	1.8	1	2	1	3	0	0
ORR	87	76.3	46	92	25	75.8	16	51.6
Total	114	100	50	43.9	33	28.9	31	27.2

CR = complete response, *PR* = partial response, *SD* = stable disease, *PD* = progressive disease, *ORR* = overall response rate

The difference in response duration was statistically insignificant either between the patients treated with rituximab as the third or subsequent line (n = 16; 16%) and first-line treated lymphoma patients (n = 46; 52.9%) or between the patients treated with rituximab as the third or subsequent line (n = 16; 16%) and second-line treated lymphoma patients (n = 25; 28.7%). However, first-line treated lymphoma patients (n = 46; 52.9%) had a significantly longer DFS (hazard ratio [HR], 0.32; 95% CI, 0.088 to 0.9, P = 0.0325) than patients treated with rituximab for the first relapse (n = 25; 28.7%). The median DFS has not been reached for any patient group treated with rituximab.

The OS from the beginning of the treatment for all 114 patients treated with rituximab and chemotherapy according to the lines of the treatment is presented in Figure 4.

First-line treated lymphoma patients (n = 50; 43.9%) had a significantly longer OS than those treated with rituximab for the first (hazard ratio [HR], 0.27; 95% CI, 0.106 to 0.645, P = 0.0036) or the second relapse (hazard ratio [HR], 0.22; 95% CI, 0.078 to 0.5, P = 0.0006). The median OS in patients treated with rituximab as the second-line treatment was 44.1 months. The median OS has not been reached for patients treated with rituximab as the first or third line of the treatment.

Discussion

We analyzed the potential influence of response quality and the line of the treatment on OS and DFS of patients with different histological types of B-cell lymphomas. Results of our study provide some evidence that response quality parallels with the survival since patients who achieved a complete response had a significantly longer OS than those reaching a partial response or those

experiencing stable or progressive disease. Yet, we must be aware that our study included both patients with indolent and patients with aggressive subtypes of lymphomas. As the two groups of B-cell lymphomas differ in their natural course, aggressiveness and above all in their susceptibility to chemo-immunotherapy, this result may have been partially influenced by the rather large proportion (36.8%) of aggressive lymphoma patients in our study. Aggressive lymphomas differ from the indolent ones as they can be to a certain extent cured with conventional chemotherapy or chemo-immunotherapy. The goal of the treatment of aggressive lymphomas is, therefore, the achievement of as many as possible complete responses in the frontline treatment since only those patients are expected to be cured.

On the other hand, up till now quite a few studies in indolent follicular lymphomas evidenced that a better response is associated with prolonged DFS yet the correlation between the quality of response and OS has not been unequivocally confirmed.[4-8] This might be at least partially on account of a rather short follow-up in these studies since an improved long-term survival for follicular lymphoma patients who reached a CR in the first-line treatment (not including rituximab) compared with patients who reached only a PR has been reported in the recently published study with a longer follow-up (median 14.9 years).[10] Also another recent study in follicular lymphoma patients treated with chemo-immunotherapy (R-CHVP-IFN) showed that the achievement of CR appears to be associated with an improved survival, although statistical significance was not reached.[13] This issue by our opinion needs a further clarification on a larger group of patients having the same histological type of lymphoma.

We also confirmed some association between the earlier rituximab treatment and longer OS and DFS. These results are in agreement with the results of our previous study reporting outcomes of the treatment with various chemo-immunotherapy combinations.[14] By that study it was confirmed that results of the treatment with rituximab and chemotherapy are in all aspects superior when the patients receive chemo-immunotherapy as the first-line treatment. The ORR was higher in the first-line treatment compared to the second or third/subsequent line treatment in patients with DLBCL, FL but not in MCL. The same was determined for DFS and OS which were longer in the first-line treatment compared to the second or third/subsequent line treatment in patients with DLBCL, FL and MCL. These observations seem logical at least in aggressive types of lymphomas where one can expect that previously untreated lymphoma patients would respond to treatment optimally as the possible mechanisms of resistance to treatment have not emerged yet.[15] The impact of the primary treatment in indolent lymphoma patients on OS might be on the other hand interfered with the second or the third-line treatments which are very likely to be needed in the course of indolent lymphomas. But in general, various other studies have also reported better survival outcomes for the frontline treatment with rituximab both in indolent and in aggressive lymphomas which was simply confirmed with our research.[16-21]

In clinical praxis, there is no doubt about how to treat patients with CD20 positive aggressive lymphomas – they should receive rituximab in front-line therapy. On the contrary, the situation in indolent lymphomas is still somehow undefined since the recommendations for the treatment of indolent lymphomas in the last few years favour the first-line treatment with rituximab. Our results, however, demonstrate that in rituximab naïve patients also the second and the third-line treatment is justifiable.

In conclusion, our data indicate that a better response to the rituximab therapy presumably translates into an improved OS and DFS for patients with B-cell lymphomas. The early introduction of rituximab into the treatment (i.e. first-line treatment) might improve OS. The proposed first-line treatment with rituximab should be considered in both types of lymphomas – the aggressive and the indolent ones. Yet, in rituximab naïve patients with indolent lymphomas also the second or subsequent line of the treatment with rituximab should be taken in account.

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research article

Second primary cancers in patients with gastric cancer

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Background. The risk of developing a second primary tumour in patients with gastric carcinoma is higher than among the general population. The aim was to investigate the clinicopathological characteristics of the second primary cancers in patients with gastric cancer in this study.

Patients and methods. In the retrospective study, patients with gastric cancers were evaluated between 1995 and 2005 for primary tumours according to Warren and Gates' criteria related with the second primary cancers.

Results. Nine of the 112 patients with gastric cancer had second primary cancers. Seven of the patients were males and two females. Six patients with gastric cancers had synchronous, and three had metachronous tumours. The age of the patients ranged from 53 to 78 years, and the mean age was 61 ± 8.3 years. The most frequent site of occurrence of the second tumours was the colo-rectum (33%) followed by the upper respiratory system (22%), and the urogenital system (22%) in descending order of frequency.

Conclusions. The incidence of the second primary cancer in gastric cancer patients was 8% in the current report. It is recommended that careful preoperative and postoperative examinations for other primary cancers, as well as for the extent of the primary gastric carcinoma, are carried out. Because colorectal cancer was the most common carcinoma combined with gastric carcinoma, the surveillance for this carcinoma (e.g., colonoscopy, abdominopelvic CT) would be appropriate after the diagnosis of gastric carcinoma.

Key words: gastric cancer; second primary cancers; synchronous cancers; metachronous cancers

Introduction

The first description of the term "multiple primary neoplasm" by Billroth in 1889 is defined as the development of more than one neoplasm in a patient.[1] Until the study of 1,259 case reports by Warren and Gates in 1932, multiple primary neoplasia were not taken seriously.[2] The increase of the average life span due to the improvement in the standard of living, the increase of exposure to carcinogens, and the positive progress in cancer prognosis result in a rise in the initiation of the second primary cancers (SPC).[3,4]

Worldwide, gastric cancer is the fourth most common cancer in population.[5,6] Nearly 70% of new cases is reported in developing countries. Gastric cancer is the second leading cause of cancer death in men and the fourth among women.[7] In Turkey, gastric cancer is the fifth most common cancer with an incidence of 10 per 100 000.[8] Recently, with new screening programs and the increase in the use of endoscopy, the early diagnosis of gastric cancer has increased and the survival has been prolonged with gastrectomy and extended lymph node dissections.[9-13]

The risk of development of a SPC in patients with cancer is increased considerably when compared to the general population.[3] Genetic, environmental and other (chemotherapy, radiotherapy etc.) factors are held responsible for the development of synchronous or metachronous (pre, post) SPC in patients with gastric cancer.

TABLE 1. Clinicopathological characteristics of patients, applied treatment methods and survivals

Age/Sex	Primary Cancer			Secondary primary cancer				
	Organ	Pathology	TNM	Organ	Time	Location	Pathology	TNM
77/M	**Stomach**	Adeno-Ca	T3N0M0	Colon	***Synchronous***	Ascending colon	Adeno-Ca	T2N0M0
58/M	**Stomach**	Adeno-Ca	T4N1M0	Kidney	***Synchronous***	Both kidneys	Renal Ca (Clear cell ca)	T2N0M0
78/M	**Stomach**	Adeno-Ca	T2N1M0	Appendix	***Synchronous***	Appendix	Mucinous carcinoma	T3N0M0
68/M	**Stomach**	Adeno-Ca	T3N0M0	Larynx	***Synchronous***	Larynx	Squamous Cell Ca	T3N1M0
54/F	**Stomach**	Adeno-Ca	T2N0M0	Pancreas	***Synchronous***	Ampulla Wateri	Adeno-Ca	T2N0M0
50/F	Colon	Adeno-Ca	T4N1MO	**Stomach**	***Synchronous*** (6 months ago)	Stomach	Adeno-Ca	T3N1M0
63/M	Bladder	Transitional cell-Ca	T2N0M0	**Stomach**	3 years ago	Stomach	Adeno-Ca	T4N1M1
53/M	Larynx	Squamosus cell-Ca	T2N0M0	**Stomach**	5 years ago	Stomach	Adeno-Ca	T4NIM0
67/F	Breast	Invasive ductal-Ca	T2N1M0	**Stomach**	3 years ago	Stomach	Adeno-Ca	T3N1M0

In this retrospective study, the aim was to investigate the frequency and clinicopathological characteristics of SPCs associated with gastric cancers.

Patients and methods

In this study, 112 patients who underwent the surgical treatment consecutively between 1995 and 2005 were evaluated retrospectively. Gastric cancer was diagnosed and confirmed by endoscopic biopsy in all patients. The patients were investigated through thoraco-abdominal imaging (CT and ultrasonography) following the routine examinations and clinical TNM staging was conducted. Clinical properties, operative findings and pathological results were evaluated from hospital records. The study were excluded those patients who were not operated on for gastric cancer due to the inoperability of their advanced gastric cancer stage.

SPC was evaluated according to Warren and Gates criteria, requiring that both tumours should be histologically malignant. There should be minimum 2 cm of tumour free tissue between the two lesions; the duration between diagnoses should be minimum 5 years if the tumours are in the same localization; and it should be demonstrated that the second tumour is not metastasis.[2] SPC is called a synchronous tumour if diagnosed at the same time with the first cancer or within the following six months, while it is called metachronous tumour if diagnosed later than six months.

Results

SPC was observed in nine of 112 patients with gastric cancer (8%). Six of these patients had synchronous cancer, while the remaining three had metachronous cancer. Seven of the patients were males and two females, and the mean age was 61.0 ± 8.3 years. According to the income, the patients had a lowest socioeconomic level and seven of them were consumed tobacco more than 20 pack-years. No data concerning the presence of malignant diseases was found in the family histories of the patients.

Six patients had *synchronous* SPC. In one patient, during the endoscopic retrograde cholangiopancreatography (ERCP) performed while aetiology of extra hepatic cholestasis was being investigated, both antrum and ampulla Vater carcinomas were observed. As the second patient was being examined for complaints such as dysphonia and dysphagia, cancer of the larynx accompanying gastric cancer was observed. During the abdominal exploration, cancer of the appendix was observed in one of the patients who underwent the surgical treat-

Operation/Procedure	Adjuvant Chemotherapy	Survivals	Cause of death
Distal esophagectomy + Proximal gastrectomy + Splenectomy + D2 Lymph dissection + Right hemicolectomy	6 courses of 5- FU + Ca Folinat	Disease free for 9 years	Alive
Distal subtotal gastrectomy + D2 Lymph dissection + Bilateral partial nephrectomy	-	22 months	Liver and pulmoner metastases (Renal cancer)
Distal subtotal gastrectomy + D2 Lymph dissection + Appendectomy	6 courses of Etoposide + Doxorubicine + Cisplatin	Disease free for 43 months	Alive
Total gastrectomy + D2 Lymph dissection + Laryngectomy + Bilateral neck dissection	Radyotherapy (Neck) 6 courses of Cisplatin + 5-FU	Disease free for 15 months	Alive
Whipple procedure	6 courses of 5-FU + Ca folinat	Disease free for 45 months	Alive
Distal subtotal gastrectomy + D2 Lymph dissection	6 courses of 5-FU + Ca folinat + 3 courses of Etoposide + Doxorubicine + Cisplatin	18 months	Brain, liver and pulmoner metastases
Laparotomy	?	4 months	Peritonitis carcinomatosa
Distal subtotal gastrectomy + D2 Lymph dissection	6 courses of 5- FU + Ca Folinat	12 months	Peritonitis carcinomatosa and liver metastasis
Distal subtotal gastrectomy + D2 Lymph dissection	6 courses of CMF + Tamoxifen	4 months	Cerebral embolisation

ment after the diagnosis of gastric cancer, while in another patient cancer of the colon was found. In a patient with gastric cancer, in the abdominal tomography performed for the preoperative evaluation, tumours were observed on both kidneys and the postoperative histopathological diagnosis was reported as renal cell cancer. The last patient in the synchronous tumour group was operated for cancer of the colon six months previously, and gastric cancer was found in the upper gastrointestinal system; endoscopy was performed during the postoperative follow-up period.

There were three patients with *metachronous* SPC: One patient had been followed in the urology department for urinary bladder cancer for three years. During laparotomy, it was found that local and at advanced stage (Stage IV). The second patient had gone through "modified radical mastectomy" due to breast cancer. In the third year of the follow up period, gastric cancer was observed. The third patient had undergone total laryngectomy and the radical cervical dissection because of cancer of the larynx five years previously.

The clinical characteristics of patients, the treatment methods and survivals are summarized in Table 1. Gastric cancer was found in three patients in the oncological follow up period. One patient had gone through right hemicolectomy for cancer of the colon six months previously. In the other five patients, the cancer was observed in the investigations done during the second malignity preoperative investigation period or in routine abdominal explorations done during the surgical treatment.

Discussion

The common use of further diagnostic methods has increased the rate of the early diagnosis of malignancy.[14] Due to the early diagnosis of cancers and current treatment methods the survival in patients with cancer has gone up recently when compared to previous years.[4] Compared with the general population, cancer patients were at a nearly increased risk for new primary cancer after cancers at many sites.[3]

In the presence of multiple cancers, there has been no discussion on the patients' prognosis being worse. However, although there have been plenty of clinical studies about such patients, the number of studies about treatment methods and how the prognosis is influenced has been quite limited. In patients with multiple cancers, cancer can be detected in different organs and their stagings are not homogenous. Furthermore, the patients cannot be classified in groups and comparative results cannot be deduced due to different methods of the treatment.

TABLE 2. The rate of gastric cancer and secondary primary cancer

	Büyükaşık O (2010)	Ikeda Y (2003)	Lee HJ (2006)	Park YK (2005)	Eom BW (2008)	Dinis RM (2002)	Muela M (2006)	Ha TK (2007)
Number of patients with gastric cancer (n)	112	2250	3291	2509	4593	2668	1170	10090
Secondary primary cancer n (%)	9 (8%)	95 (4.2%)	111 (3.4%)	65 (2.6%)	159 (3.4%)	78 (3.4%)	23 (1.96%)	96 (%1.0)
Synchronous tumours	6 (66%)	48 (50.5%)	111 (100%)	17 (26.2%)	49 (30.8%)	21 (27%)	12 (52%)	96 (%100)
Metachronous tumours	3 (33%)	47 (49.5%)		48 (73.8%)	110 (69.2%)	57 (73%)	11 (48%)	
Pre metachronous	3 (33%)			36 (55.4%)	42 (26.4%)			
Post metachronous	0			12 (18.4%)	68 (42.8%)			

It is well known that synchronous and/or metachronous cancers can be observed in the same or different organs. These include oesophageal with oropharyngeal cancer or gastric carcinoma, breast carcinoma with contralateral breast carcinoma or endometrial carcinoma, colon and rectal carcinoma with another colorectal primary or genitourinary primary tumour, and multiple primary cancers within the urinary tract. It is thought that the presence of cancer in the family history, genetic factors and chemotherapy and radiotherapy applications affect the formation of multiple cancers. Despite the fact that there have been studies showing that the synergy of gastric cancer and other cancers can be due to certain disorders, such as microsatellite instability, germ-line mutations and E-cadherin, TP53, RAS mutation; the molecular basis of the formation of tumours is still not understood completely.[15-17]

The frequency of SPC-associated gastric cancer was found as 8% in the current study. As it can be seen in Table 2, in previous studies this rate varies between 1 and 4.2%.[9,10,18-23] Our incidence was higher than that of other reports. In this study, the number of patients with second primary cancers is small and thus important statistical limitations exist. A better improved national cancer record system and broader series are required. However, this higher incidence might be due to the fact that this study analyzed patients who had undergone surgical intervention. On the other hand, in order to draw attention to the fact that the frequency of SPC in Turkey is higher than other societies

Concerning second primary cancers in gastric cancer patients, environmental factors, such as dietary habits or tobacco use, and genetic factors have also been suggested to be risk factors. In published series, it is seen that the frequency of finding SPC accompanying gastric cancer is higher in older male patients, as it is in other types of cancer.[3,10,18,22] In the series presented, the mean age was 61.0 ± 8.3 (Min 53 - Max 78), the male/female ratio was 7/2. It is accepted that smoking is an important risk factor for multiple primary cancers just as in other types of cancers. In this study, it was observed that 78% of the patients consumed tobacco.

The tumour determining the prognosis in SPC is gastric cancer.[16] However, second malignancies in patients with early gastric cancer have a determinant effect on prognosis.[22] The method of the treatment of synchronous cancers should include the primary cancer about which malignancy prognosis is expected. Synchronous cancer should be treated with curative intent if possible.[5]

In a study in which gastric cancer was investigated as the SPC, an increase in gastric cancer development risk was observed within 10 years following cervical, ovarian, testicular cancers and Hodgkin and non-Hodgkin lymphoma. Treatments of the initial cancer, such as the radiation therapy or chemotherapy were found to be responsible for this increase in risk in gastric cancer and SPC.[24] It is stated that the highest risk is after esophagus cancer in sporadic patients.[5] In the patients followed in the current study, gastric cancer developed as SPC following breast, larynx and bladder cancer. These are sporadic cases.

Hereditary conditions known to increase the risk of gastric cancer include: familial cancer syndromes such as hereditary non-polyposis colorectal cancer, Li-Fraumeni syndrome, breast-ovarian cancer syndrome, multiple endocrine neoplasia Peutz-Jegher syndrome and Cowden syndrome.[2] In hereditary cancers, the average age of onset for the gastric cancer is in the late 30s with the majority of cancers occurring before age 40.

Among the SPCs associated with gastric cancer, colorectal cancers are the most frequent and their rate is reported to be between 20% and 70%.[19,21] In our study, synchronous colorectal cancer was found (33.3%) in three patients (of the colon in two patients and of the appendix in one patient). It is

reported that lung cancer is the second most frequently occurring cancer among all SPCs.[3,9,18,19,21] Many researchers state that performing gastroduodenoscopy and colonoscopy is necessary in the preoperative evaluation and in the postoperative follow up of patients with gastric and colorectal cancers; whereas some researchers suggest that bronchoscopy should be added to these investigations.[14,21,25]

In the present series, the rate of SPC associated with gastric cancer is 8%. This relatively high rate indicates that it would be highly significant to pay attention to the development of SPC in the preoperative evaluation period, in the exploration during surgery, and in the postoperative follow up period. The systemic investigation and examination of patients with gastric cancer should be performed in detail, and all organs should be examined carefully during surgery. In addition, while investigating possible recurrence and metastasis of the primary cancer, all systems should be examined for the possible presence of SPC. Not only for patients with gastric cancer, but also for all malignant cases it is extremely necessary to inform the patients about signs and symptoms of other organs and to perform the systemic investigation and the full physical examination in each control in case multiple primary cancers develop. The early diagnosis of SPC provides a longer survival and a better quality of life.

To conclude, the probability of the development of multiple primary cancers should be considered in the diagnosis and the treatment of all malignant tumours. Since gastric and colorectal cancer synergy is quite frequent, the importance of gastrointestinal panendoscopy should be highlighted. The treatment should be appropriate for observed synchronous or metachronous cancer and it is necessary to try to be treated with curative intent in combined radical resections.

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research article

Lymphedema following cancer therapy in Slovenia: a frequently overlooked condition?

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Introduction. Secondary lymphedema following cancer therapy is a frequent, often painful, quality of life disturbing condition, reducing the patients' mobility and predisposing them to complications, e.g. infections and malignancies. The critical aspect of lymphedema therapy is to start as soon as possible to prevent the irreversible tissue damage.

Patients and methods. We performed a retrospective study of patients with lymphedema, treated at the Department of Dermatovenereology, University Medical Center Ljubljana, from January 2002 to June 2010. The patients' demographic and medical data were collected, including type of cancer, type and stage of lymphedema, and time to first therapy of lymphedema. The number of referred patients with lymphedema following the therapy of melanoma, breast cancer, and uterine/cervical cancer, was compared to the number of patients expected to experience lymphedema following cancer therapy, calculated from the incidence reported in the literature.

Results. In the period of 8.5 years, 543 patients (432 females, 112 males) with lymphedema were treated. The results show that probably many Slovenian patients with secondary lymphedema following cancer therapy remain unrecognized and untreated or undertreated. In the majority of our patients, the management of lymphedema was delayed; on average, the patients first received therapy for lymphedema 3.6 years after the first signs of lymphedema.

Conclusions. To avoid a delay in diagnosis and therapy, and the complications of lymphedema following cancer therapy, the physician should actively look for signs or symptoms of lymphedema during the follow-up period, and promptly manage or refer the patients developing problems.

Key words: lymphedema, secondary lymphedema; cancer therapy, adverse effects; radiotherapy, adverse effects

Introduction

Lymphedema is swelling due to excess accumulation of lymph in the tissues caused by inadequate lymph drainage. Lymphedema differs clinically form other forms of chronic edema by its altered skin texture and brawny quality of the subcutaneous tissues which limit pitting. Primary lymphedema implies a genetic or constitutive cause whereby there is an intrinsic fault in the lymph drainage determined by the lymphatic maldevelopment or functional weakness. Secondary lymphedema implies an acquired failure of previously normal lymph drainage due to an identifiable cause extrinsic to the lymphatic system.[1] Secondary types of lymphedema are more common than the primary ones. In developed countries, cancer treatment dominates as a cause, whereas in tropical climates lymphedema is usually due to infections.[2]

The reports on worldwide incidence of lymphedema following cancer therapy in the available literature are scarce and varying considerably. The estimated incidence of breast cancer-related lymphedema is ranging from 13-50%.[3-5] The introduction of sentinel lymph node biopsy reduced the incidence of lymphedema, however not as dramatically as it was hoped.[1] The incidence of lower limb lymphedema following radical hysterectomy alone is estimated at 5-10% but can be as high as 49% by 10 years of follow-up in patients who also received the adjuvant radiation treatment.[6-7] The incidence of lymphedema after lymphadenectomy

TABLE 1. Staging of lymphedema

Stage	Clinical findings	Stemmer's sign
0	Latent phase – no edema	Negative
I	Soft edema	Negative
II	Initially: pitting edema; Longstanding: elastic edema	Positive
III	Hard, enormous edema, skin changes	Positive

TABLE 2. Number of patients by type of edema

Total: 543 patients (432 females, 112 males)		
Primary lymphedema 139 patients	Secondary lymphedema 404 patients	
	Following cancer therapy 227 patients (198 females, 29 males)	Due to other causes 177 patients

TABLE 3. Lymphedema by localizations

776 localizations of lymphedema in 543 patients	
498 localizations of lymphedema due to a non-malignant cause	278 lymphedemas following a malignant disease
483 edemas of the lower extremity 15 edemas of the upper extremity	199 edemas of the lower extremity 72 edemas of the upper extremity 2 facial edemas 2 trunk edemas 1 scrotal edema 1 penile edema 1 breast edema

for melanoma can be up to 44% after therapeutic groin dissection for palpable disease,[8] but the incidence following sentinel lymph node biopsy is much less.[7,9]

There are no available epidemiological reports of lymphedema following cancer surgery in Slovenia. A decade ago, an outpatient office specialized in lymphedema was introduced at the Department of Dermatovenerology, University Medical Center Ljubljana. As this is the only specialized center of this type in Slovenia, the number of referred patients is constantly increasing. Besides providing the best of care for these patients, one of the future aims of the center is to establish a national registry of lymphedema to provide epidemiologic data.

The clinical staging of lymphedema is shown in Table 1. Latent or subclinical (stage 0) lymphedema, even after surgical lymphadenectomy, may persist for months to years without any clinical evidence of lymphatic disturbance. Trigger events, e.g. insect sting, physical exertion, injuries, inflammation or warming of the limb may cause edema, which is either reversible or may, with additional lymphatic overload, proceed to the following stage. In stage I, the edema is reversible, soft, disappearing spontaneously overnight or, with compression therapy, during the day. The skin is smooth, with small pits. Stage I may persist for several years. However, if left untreated, it sooner or later proceeds to the chronical stage II.

During the stage II, edema persists despite limb elevation. In the early stage, edema is still pitting, later the edema is non-pitting, elastic. The skin feels harder, fibrotic. This phase cannot be reversed spontaneously without therapy. The Stemmer's sign is positive – the skin on dorsal surface of the second toe cannot be pinched into a fold.

During the stage III (*elephantiasis*) the edema is enormous. The skin shows trophic changes (fibrosis, hyperkeratoses, papillomatosis, hyperpigmentations, lymphorea, ulcerations) and is prone to bacterial and fungal infections. The condition may

TABLE 4. Malignancies that caused lymphedema in our patients, by the year of first referral

	Year									
Cause	2002	2003	2004	2005	2006	2007	2008	2009	2010 (Jan-Jun)	Total
Breast cancer	1	2	2	12	6	3	6	22	14	68
Uterine and cervical cancer	6	9	13	8	9	7	3	11	1	67
Melanoma	2	3	2	3	4	6	4	10	7	41
Sarcoma	1	1	1	1	1	1	1	2	1	10
Colorectal cancer	1	2	0	0	0	2	0	2	1	8
Post-radiotherapy for lymphoma	0	1	1	1	1	1	1	0	1	7
Vulvar cancer	0	0	1	2	0	1	1	1	0	6
Prostatic cancer	0	1	0	0	0	0	0	2	2	5
Ovarian cancer	1	0	0	1	0	0	2	0	0	4
Lymphadenectomy for unknown cancer	1	0	0	0	0	1	1	1	0	4
Testicular cancer	0	0	1	1	0	0	0	0	1	3
Bladder cancer	0	0	1	0	0	0	0	1	0	2
Lung cancer	0	0	0	0	1	0	0	0	0	1
Non-melanoma skin cancer	0	0	0	0	0	0	1	0	0	1
Total	13	19	22	29	22	22	20	52	28	227

only partly improve with the appropriate therapy. Occasionally, development of highly malignant lymphangiosarcoma or other malignancies may ensue.[1,10-12]

Pain may be present during all stages. The patients also report numbness, feeling of heaviness, fatigue, paresthesias, or mobility disturbances of the affected limb.[10-12]

Irreversibility of the later stages of lymphedema calls for timely therapeutic intervention. The delay in seeking medical attention for lymphedema by the patient, as well as the physicians' unawareness or underestimation of the condition might lead to chronic, hard to manage problems. During follow-up after cancer surgery and/or radiotherapy, the physician should actively look for signs or symptoms of lymphedema, and promptly manage or refer the patient developing problems.

As in case of other side effects following cancer therapy, the therapy of lymphedema should be tailored individually.[13] It should consider the patient's clinical situation, history, and any coexisting illnesses. The patient's compliance is of crucial importance. Therefore, the continuous patient education and encouragement are essential parts of the management.

Edema should be reduced as early as possible, using the compression therapy and/or manual lymph drainage. During improvement, compression stockings are required to maintain the improved condition.[11,12,14-17]

The opinions and studies on drug therapy for lymphedema are controversial. Invasive approaches may be appropriate only in a minority of patients. Surgery may cause further damage to lymphatics, and lead to ulceration, fistulas, skin necrosis and exacerbation of edema.[12]

The recommended additional measures include mobilization to improve the muscle pump function. Extreme heat, cold, and trauma should be avoided. Proper skin care to prevent infections is also an important part of the management.[11]

Patients and methods

We performed a retrospective study of patients with lymphedema treated at the Department of Dermatovenereology, University Medical Center Ljubljana, from January 2002 to June 2010. The patients' charts were reviewed, and the following data were collected: demographic data, type of malignancy, year and type of the oncologic procedure, type, location and stage of lymphedema, time of appearance of lymphedema after the procedure, and duration of lymphedema before the first intervention. The average time of appearance of lymphedema after the procedure and the aver-

TABLE 5. Slovenian total incidence of melanoma, breast cancer, and uterine/cervical cancer in 2002–2007[18], compared to the number of patients expected/referred for lymphedema after procedure for cancer. *Expected number of patients with lymphedema after therapy for the relevant condition, according to the published reports[3-9]

	Year					
	2002	2003	2004	2005	2006	2007
Melanoma						
Total incidence	148	202	210	226	395	437
Expected patients with lymphedema (N)*	65	88	92	99	173	192
Referred patients with lymphedema (N)	2	3	2	3	4	6
Breast cancer						
Total incidence	817	856	911	944	1117	1153
Expected patients with lymphedema (N)*	106-408	111-428	118-455	122-472	145-558	149-576
Referred patients with lymphedema (N)	1	2	2	12	6	3
Uterine/cervical cancer						
Total incidence	449	467	476	480	442	449
Expected patients with lymphedema (N)*	22-220	23-228	24-233	24-235	22-216	22-220
Referred patients with lymphedema (N)	6	9	13	8	8	7

age duration of lymphedema before the first intervention were calculated by using simple statistical methods. The expected incidence of lymphedema following melanoma, breast cancer, and uterine/cervical cancer was calculated from the incidence reported in the Slovenian cancer registry in the years 2002–2007[18], and compared to the worldwide lymphedema incidence reports[4-9], by using simple statistical methods.

Results

In the period of 8.5 years, 543 patients (432 females, 112 males) with lymphedema were treated. Of the 543 patients, 139 patients presented with primary and 404 with secondary lymphedema in 776 localizations. Secondary lymphedema following cancer therapy was found in 227 patients. Details are shown in Tables 2 and 3.

The average time from cancer therapy (surgery or/and radiotherapy) to the development of lymphedema was 3.4 years. In 112 patients, edema started shortly after the procedure, however, maximal time to the development of lymphedema was 31 years after the cancer therapy in one patient. The average time from the appearance of lymphedema to start of the therapy for lymphedema was 3.6 years. Only three patients received therapy for lymphedema as soon as the edema started, and maximal time from beginning of lymphedema to therapy was 28 years. The average time from cancer intervention to start of lymphedema therapy was 7 years, maximum 39 years. Only one patient received the therapy for lymphedema immediately after the procedure for cancer.

The causes of lymphedema in our oncologic patients are shown in Table 4, by the year of the first referral.

The number of patients referred for lymphedema following cancer therapy for melanoma, breast cancer, and uterine/cervical cancer from 2002 to 2007, and the comparison to the expected incidence of lymphedema is shown in Table 5.

Discussion

The reports on the worldwide incidence of lymphedema following cancer therapy in the available literature are scarce and varying considerably. Until present, there were no available epidemiological reports of lymphedema following cancer surgery/radiotherapy in Slovenia.

The majority of patients with secondary lymphedema following cancer referred to Department of Dermatovenerology during the observed period were patients with lymphedema of the lower ex-

tremities following uterine/cervical cancer, patients with lymphedema of the upper extremity following breast cancer, and patients following lymphedema after procedure for melanoma, accounting together for 77.5% of all patients with secondary lymphedema following cancer. The management of lymphedema in the included patient population was delayed; the patients first received therapy for lymphedema on average 3.6 years after the first signs of lymphedema and on average 7 years after the procedure for cancer.

Calculated from the reported incidence of cancer in Slovenia[18] and the reported worldwide incidence of lymphedema due to cancer[4-9], the expected incidence of lymphedema in Slovenia during the period 2002-2007 following melanoma, breast cancer, and uterine or cervical cancer is much higher than the actual number of patients referred to the Department of Dermatovenerology during this period. Since the Department features the only specialized center for lymphedema in Slovenia, it can be possibly concluded that many patients with lymphedema after cancer therapy remain unrecognized and untreated or undertreated.

Beside the adequate choice of the oncological treatment option[19,20], the physician should actively look for signs or symptoms of lymphedema during the follow-up of patients. If lymphedema after cancer surgery and/or radiotherapy is observed, the patient developing problems should promptly be referred. Lymphedema during the early stages is a reversible or partially reversible state, whereas it is irreversible and very hard to manage if left to proceed to the late stages, causing great patient disability and predisposing them to complications, eg. infections and malignancies. The results of the present study also emphasize the need to establish a Slovenian national registry of lymphedema.

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research article

Evaluation of clinical interventions made by pharmacists in chemotherapy preparation

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Background. Cancer drugs are high risk drugs and medication errors in their prescribing, preparation and administration have serious consequences, including death. The importance of a multidisciplinary approach and the benefits of pharmacists' contribution to cancer treatment to minimise risk have been established. However, the impact of services provided by pharmacists to cancer patient care is poorly studied. This study explored the clinical interventions made by pharmacists in dispensing of chemotherapy doses, and evaluated pharmacists' contribution to patient care.

Methods. Pharmacists at the Chemotherapy Preparation Unit at a tertiary cancer centre in London were shadowed by two research pharmacists during the clinical screening of chemotherapy prescriptions and release of prepared drugs. An expert panel of pharmacy staff rated the clinical significance of the recorded interventions.

Results. Twenty-one pharmacists' interventions were recorded during the screening or releasing of 130 prescriptions or drugs. "Drug and therapy" (38%), "clerical" (22%) and "dose, frequency and duration" (19%) related problems most often required an intervention, identifying areas in chemotherapy prescribing that need improvement. The proposed recommendations were implemented in 86% of the cases. Many recorded interventions (48%) were ranked to have had a "very significant" influence on patient care.

Conclusion. Clinical interventions made by pharmacists had a significant impact on patient care. The integration of pharmacists' technical and clinical roles into dispensing of chemotherapy doses is required for providing high-quality cancer services.

Key words: pharmacy; cancer; chemotherapy; drug compounding; medication errors

Introduction

Cancer drugs, involved in 15.4% of reported fatal cases, are second only to drugs acting on the central nervous system in medication error associated mortalities.[1] High toxicity of cancer drugs is not problematic only when these medications are used inappropriately, but life-threatening side effects may occur also during regular treatment - their use requires clinical expertise.[2] Thus, cancer drugs are defined as high risk drugs; the prescribing, preparation and administration of which require special regulation and the collaboration of different healthcare professionals.[3,4] Pharmacists have a central role in guaranteeing the safe, effective and economic use of cancer drugs.[3-8]

The dispensing of cancer drugs in designated centralized chemotherapy preparation pharmacy units has been extensively studied to improve its quality and minimise personnel exposure to these drugs.[4-7] As a result, the technical roles, responsibilities and duties of pharmacists in the dispensing of chemotherapy doses are well defined.[5-7] However, the same cannot be said of the clinical role of pharmacists. Although this role has been described to some extent in the Competency

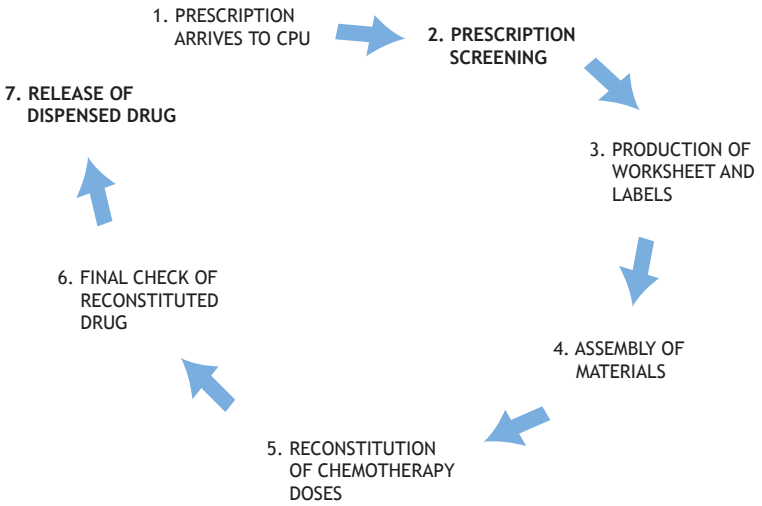

FIGURE 1. Stages in dispensing of cancer drugs in the Chemotherapy Preparation Unit (CPU). The study observed pharmacists during the stages of prescription screening and release of dispensed drugs; stages where only technical interventions were expected or where pharmacy technician and assistants were participating were not covered in the study.

Framework for Specialist Oncology Pharmacists of the British Oncology Pharmacists Association and in the German Quality Standard for the Pharmacy Oncology Service as well as emphasised in numerous studies, the clinical services provided by pharmacists in chemotherapy dose dispensing are not standardised across Europe.[7-11] This may lead to substantial variation in the quality of patient care.

As a consequence of being poorly defined, pharmacists' clinical services in chemotherapy dose dispensing are also poorly studied. The implementation and benefits of these services have been described in several reports;[4,9-12] however, pharmacists' contribution to patient care is rarely assessed. Only a recent report of the British National Confidential Enquiry into Patient Outcome and Death (NCEPOD) provided evidence on the extent of pharmacists' contribution to patient outcomes.[11] The report analysed the treatment of cancer patients who had died within the first 30 days after receiving systemic chemotherapy. Finding that only half of chemotherapy prescriptions of these patients had been checked by a pharmacist, the NCEPOD highlighted this service as one of the measures required to reduce the risk of death after receiving systemic chemotherapy. The evaluation of current practices and the evaluation of the impact of changes in routine practices on patient care are important in all fields of oncology.[13]

This study aimed to explore clinical interventions made by pharmacists in dispensing chemotherapy doses, and to evaluate their significance for patient care.

Methods

Study design and sample

The study was designed as a prospective, descriptive, cross-sectional study of interventions made by pharmacists in dispensing of chemotherapy doses. The study complements another study that focused on exploring interventions made by pharmacists when providing routine clinical pharmacy services on cancer wards.[14] The study was conducted at the Chemotherapy Preparation Unit (CPU) at St. Bartholomew's Hospital, London, UK, a tertiary cancer centre. Ethics approval was not required as the study was part of the Trust's service development. However, the study protocol was reviewed by two independent researchers at the School of Pharmacy, University of London, to assess any ethical issues.

The study evaluated interventions made by pharmacists during their daily routine practice in chemotherapy dose dispensing in a hospital setting (Figure 1). The study focused on the two stages in this process that can be performed only by pharmacists: screening of prescriptions; and release of dispensed drugs.

During prescription screening, pharmacists checked the correctness of clerical data, dose calculation, dose adjustment in altered essential pre-treatment investigation data, time and mode of administration and prescription of supportive therapy for expected toxicities. Before the release of a drug, pharmacists had to verify the correctness of the overall procedure and the quality of the dispensed drug.[5] An intervention, such as adjusting a chemotherapy dose or adding supportive therapy, may be required at any point of the described processes. Both stages were observed at different times and independently of each other. Four clinical oncology pharmacists and one advanced clinical oncology pharmacist were working at the CPU at the time of the study.

Developing the data collection form and collecting data

A literature review on potential medication errors and pharmacists' clinical interventions[12-19], observations of pharmacists' work at the CPU, discussions with pharmacy practitioners and academic supervisors served as the basis for the development of a data collection form for recording and classifying the interventions. Interventions may be required due to various problems. Depending on the identi-

TABLE 1. Description of the recorded interventions and their clinical significance

SIGNIFICANCE FOR PATIENT CARE		INTERVENTION
Expert panel	**Medical consultant**	
Potentially life saving	Potentially life saving	Trastuzumab is ordered for a patient, who has experienced a serious adverse drug event during previous administration.
Very significant	Potentially life saving	Chemotherapy is ordered 7 days ahead of protocol.
	Very significant	Impaired hepatic function requires dose modification of paclitaxel.
	Very significant	Etoposide dose was miscalculated when switching from oral to intravenous route of administration.
	Very significant	Impaired renal function requires dose modification of cisplatin.
	Significant	Impaired renal function requires dose modification of carboplatin.
	Significant	Chemotherapy is ordered as 6th cycle whereas it was patient's 4th cycle.
	Significant	Chemotherapy order is not signed by the medical practitioner.
	NA*	Impaired renal function requires dose modification of fludarabin.
	NA	Grade 3 neutropenia require chemotherapy to be postponed.
	NA	Full dose of irinotecan is ordered although patient received modified doses in previous cycles.
Significant	Very significant	Two chemotherapy orders with different information on body surface area are received for the same patient.
	Significant	Cancer drug that is per protocol given every week interval is ordered every fortnight.
	Significant	The chemotherapy order does not include the required antiemetic therapy.
Minor significance	Potentially life saving	The name of the patient on chemotherapy order is illegible.
	Potentially life saving	Cancer drugs for iv and it administration are prescribed on same chemotherapy order.
	NA	The order for the last chemotherapy is not recorded in the CPU† patient file.
	NA	Incorrect information of a patient's height.
	NA	Wrong calculation of the body surface area.
	NA	Grade 3 neutropenia require chemotherapy to be postponed.
	NA	Etoposide is instable in the ordered infusion volume.

* NA (not applicable) the medical consultant did not assess the clinical significance of interventions for patient care
† CPU stands for Chemotherapy Preparation Unit

fied problem, an intervention could be classified to be required due to "a clerical problem", for example, missing patient or administrative data, "a drug and therapy problem", for example, omission or commission of drugs, or presence of a contraindication for the prescribed drug, "a dose, frequency and duration problem", for example, inappropriate dose calculation or need for dose adjustment, wrong time or duration of the chemotherapy or "an administration and formulation problem", for example, formulation or administration discrepancies with agreed treatment protocols.

The data collection was carefully planned. While the observation times were randomly selected, they allowed observations during six morning and three afternoon shifts on five different week days, taking into account potential variation in workload. The data were collected by two research pharmacists, who independently observed, without interfering, the clinical pharmacists' work; this method has been found to be superior to self-reporting by healthcare professionals in medication error research.[20]

Rating the significance of interventions

An expert panel of four members of pharmacy staff (the head of preparation services, two clinical oncology pharmacists and a specialist in drug manufacture and drug stability) was first asked to individually rate the interventions' significance to patient care (patient safety) using a five-point Likert scale (Table 1).[20] The clinical significance of the recorded interventions was then determined using a modified nominal group consensus method[20], each panellist's opinions were presented and discussed until the panel reached a consensus. To further validate the panel's decisions, a consultant in medical oncology independently ranked the clinical significance of a sample of 13/21 (60%) interventions that

TABLE 2. Characteristics of recorded interventions

Parameter	Category	n	%
Number of recorded interventions	Number of observations	130	
	Number of interventions	21	
BNF* group of drug involved	Malignant diseases & immunosupression	27 / 29†	93 %
	• Antimetabolites	6 / 29†	21 %
	• Anthracyclines & other cytotoxic antibiotics	5 / 29†	17 %
	• Vinca alkaloids & etoposide	4 / 29†	14 %
	• Other antineoplastic drugs: Taxanes	4 / 29†	14 %
	• Other antineoplastic drugs	8 / 29†	28 %
	Drugs outside malignant disease & immunosupression group	2 / 29†	7 %
Identified drug related problem	Drug and therapy	8 / 21	38 %
	Clerical	7 / 21	33 %
	Dose, frequency and duration	4 / 21	19 %
	Administration and formulation	2 / 21	10 %
Contacted healthcare professional	Clinician	13 / 21	62 %
	Nurse	2 / 21	10 %
	None	6 / 21	29 %
Implementation of the intervention	Implemented	18 / 21	86 %
	Implemented, with amendments	1 / 21	5 %
	Not implemented	2 / 21	10 %

* BNF stands for British National Formulary
† one intervention could involve more than one drug

were selected using a list of randomly generated numbers (Table 1).

Data handling and statistical analysis

Confidentiality of patients and pharmacists was observed in handling the collected data and no names were recorded. The data on the recorded interventions were coded and entered onto an SPSS (version 14) database. Data are presented as frequencies and proportions; median values and ranges are presented where possible. Associations and differences between variables were explored using non-parametric tests: Chi square, Mann-Whitney U and Kruskal-Wallis H test, as appropriate.[21]

Results

At the time of the study, the CPU received an average of 230 chemotherapy orders daily. Five pharmacists were observed during the screening of 85 prescriptions and the release of 45 drugs (Table 2). Overall, 21 interventions, which concerned 29 drugs prescribed for 18 patients, were recorded: 19 during prescription screening (19/85; 22%) and two during drug release (2/45; 4%).

Patient characteristics

Patients, whose treatment required an intervention, had a median age of 49 years, ranging from 24 to 75, and most were female (15/18; 83%) (Table 3). More patients were treated for solid tumours (12/18; 67%) than for haematological malignancies. Patients were treated with standard chemotherapy (14/18; 78%) or received clinical trial treatment (4/18; 22%) and two patients received concomitant treatment with radiotherapy (2/18; 11%).

Intervention characteristics

The identified problems were often related to "drug and therapy" (8/21; 38%), followed by "clerical" (7/21; 33%) and "dose, frequency and duration" (4/21; 19%) issues whereas "administration and formulation" problems (2/21; 10%) required an intervention of a clinical nature less often (Table 2). Some interventions (6/21; 28%) were required due

TABLE 3. Characteristics of patients

Characteristic		n	%
Sex	Female	15 / 18	83 %
	Male	3 / 18	17 %
Diagnosis	Solid tumours	12 / 18	67 %
	• Lung cancer	4 /18	22 %
	• Breast cancer	3 / 18	17 %
	• Other solid tumours	5 / 18	28 %
	Haematological malignancies	6 / 18	33 %

to altered pre-treatment investigation data, for example, changes in drug doses were required because of out of range blood test results, or deteriorating renal or liver function.

Certain problem types, for example, altered investigation results, were often found to require similar interventions to rectify the problem, resulting in pharmacists making similar recommendations, for example, proposing a dose modification (Table 1). The identified problem and proposed recommendation were discussed, if needed, with the responsible clinician (13/21; 62%) or nurse (2/21; 10%). Most interventions (18/21; 86%) were implemented as recommended (Table 2). One was implemented with an amendment – instead of reducing the dose of carboplatin due to altered renal function, the clinician decided to postpone the chemotherapy cycle. In two cases the interventions were not accepted. In the first case, postponing of the chemotherapy treatment of a patient with grade three neutropenia had been recommended. A clinician argued that despite the chemotherapy having been previously postponed and the dose reduced the neutropenia had been persistent; thus, the patient should be treated. In the second case, while halving the dose of paclitaxel had been recommended due to altered hepatic function, a clinician offered no reason for not reducing the dose.

Most interventions concerned cancer drugs (27/29; 93%) than supportive therapy drugs. Since all cancer drugs are renowned as high risk drugs, pharmacists' interventions prevented serious consequences of errors in their use. Some interventions did not involve any drug (5/21; 24%) (Table 2).

Significance of the recorded interventions for patient care

The expert panel rated the interventions made by pharmacists: three had "significant" (14%); 10 "very significant" (48%); and one "potentially life saving" (5%) impact on patient care, preventing detrimental effects on the patients (Table 1). Moreover, the consultant in medical oncology independently ranked all of the 13 randomly selected interventions to be at least "significant" for patient care and gave exactly the same rating as the expert panel in six of 13 cases (Table 1). The consultant considered two interventions rated by the expert panel as having "minor significance" to patient care to be "potentially life saving"; these were the only two interventions where the rating differed by more than one category. The significance of recorded interventions was not associated with any patient characteristic or drug involved; no patient or drug subgroup was identified to be at greater risk of potential medication errors that would require greater vigilance.

Pharmacists were more likely to independently solve problems of minor significance, whereas they worked with clinicians and nurses to implement interventions of higher significance (Kruskal – Wallis, X^2=10.686, df=2, p=0.005). Drug related problems related to "drug and therapy" and "dose, frequency and duration" were more likely to require interventions of higher significance than those related to "clerical" and "administration and formulation" issues (Kruskal – Wallis, X^2=8.003, df=3, p=0.046).

Due to resource restraints it was not possible to observe all interventions made by pharmacists in one week. However, if the data are extrapolated on the weekly average of 230 chemotherapy prescriptions, pharmacists are expected to make approximately 50 interventions during prescription screening and ten during the release of dispensed drugs. Based on this estimation and the significance of the observed interventions, three drug related problems with potential fatal consequences may be prevented every week.

Discussion

This study provided evidence of the contribution of the clinical pharmacists in the dispensing of chemotherapy doses to the safety of patients.

Strengths and limitations

Studies of self-recorded clinical interventions may underestimate the frequency of required interventions[20]; in this study data were collected by independent researchers, providing a more complete picture of the interventions. Moreover, the expert panel reached consensus on the significance of the recorded interventions. However, the study presents some limitations.

This cross-sectional study was limited to nine visits in a centralized CPU at one hospital. The results may not be representative, but the study aimed at providing insight into pharmacists' clinical interventions in dispensing of chemotherapy doses. The low number of visits was accepted as a limitation in exchange to having the data collected by independent observers. While the impact of pharmacists' intervention on patient care was determined by an expert panel of pharmacy staff, one medical consultant separately evaluated the interventions, mainly confirming the panel's decisions. Furthermore, the high level of significance assigned to the interventions by the consultant and the high proportion of implemented interventions suggest a high level of agreement and further confirm the need for similar services.

Findings

The number of recorded interventions and their significance show that pharmacists contribute to patient care, which confirms the importance of their role in managing the risks associated with cancer drugs. Pharmacists' interventions on prescribed chemotherapy observed on the wards and good and accurate risk management procedures in the dispensing of chemotherapy doses, such as the use of pre-written chemotherapy prescriptions, may have lowered the number of interventions needed as confirmed in the literature.[4,9-11,14,22]

The rate of interventions in the present study, 22% during prescription screening and 4% during drug release, was higher than the rate of medication errors identified in chemotherapy prescription orders reported in the literature.[9,11] Markert *et al.* reported a chemotherapy error in 17.1% of received chemotherapy orders[9], while Slama *et al.* reported a prescribing error in 12% of the received chemotherapy orders.[11] However, the majority of errors in the described studies, 50.9% and 74%, respectively, were related to problem categories not included herein: missing a patient's informed consent; and physicochemical incompatibilities. The lower proportion of recorded interventions in the literature may be attributed to differences in the duties of pharmacists in the dispensing processes in different countries or to discrepancies in the methodology of the studies.

The problems identified in the recorded interventions indicate areas in the chemotherapy prescribing practice that need improvement: writing of a chemotherapy order; and adjusting the dose according to blood and biochemistry data. Pharmacists were often observed to recommend changes to chemotherapy prescriptions that contained incorrect information; a problem that has been reported in the literature.[9,11,23] Correct patient details on weight and height are of utmost importance for the correct calculation of the chemotherapy dose. Computerised chemotherapy order forms have been shown to diminish the number of errors[4,5,9,10,24]; while the possibilities for the implementation of computerised prescribing should be investigated, the limitations and problems of similar systems should be acknowledged.[25,26]

The individual dosing of cancer drugs and their important toxicity profile require constant monitoring of the health status of the patient. In this study, dose adjustment due to altered blood count, renal or hepatic function test results was the most common intervention, preventing the occurrence of potential adverse events with detrimental effects on the patient. This confirms the importance and need of pharmacists' clinical knowledge in dispensing of chemotherapy doses. Moreover, the two interventions observed during the release of drugs also recommended a dose adjustment due to a change in patients' renal or hepatic function. In both cases, the essential pre-treatment investigation data had not been available at the time of prescription screening, thus, to avoid a delay in dispensing the chemotherapy dose, the order was forwarded to the preparation room without this check, and the investigation data were available and checked only before the release of the drug, when the need for dose adjustment was identified. While most interventions (90%) have occurred before the release of drugs, such practice may result in the disposal of a dispensed drug and their re-dispensing; thus, the timely availability of essential pre-treatment investigation data may not have only safety, but also

substantial economic implications. The literature shows that checking of chemotherapy doses with essential pre-treatment investigation has not been clearly stated as obligatory in many settings.[7,9,11,23] However, the results of the present study imply that this service should be integrated into the dispensing of chemotherapy doses.

Pharmacists made highly significant interventions, showing the value of their contribution to cancer services. No patient characteristic or drug group was identified to require special interventions, perhaps due to low numbers of observations. The harm of medication errors in chemotherapy prescribing requires maximal risk control mechanisms *per se*, regardless of the treated patient or used drug. When dealing with problems of greater significance such as a contraindication for the prescribed treatment or a need for dose adjustment, pharmacists consulted nurses and clinicians. Clinicians agreed with most of the proposed interventions, confirming their importance also from a medical perspective. Good and well established collaboration between all healthcare professionals should be routine to prevent drug related problems from occurring in chemotherapy treatment.

The benefits of good collaboration are not restricted to chemotherapy dose dispensing. In fact, the collaboration between pharmacists and clinicians on the wards together with the tight regulation of the dispensing of chemotherapy doses may have solved problems of mainly minor significance[14], before they reached the CPU. This, in addition to the fact that most interventions involved cancer drugs that are by definition high risk drugs, may have contributed to the high clinical significance of the recorded interventions. The integration of the work of pharmacists on the cancer wards and at the CPU is a great advantage for patient care.

To our knowledge, this study is the only study evaluating the impact of pharmacists' clinical interventions in dispensing of chemotherapy doses on patient care. Studies describing pharmacists' services in dispensing of chemotherapy doses either did not evaluate their impact on patient care or the contribution to patient care was done *a priori*, according to the detected medical error.[4,9,11,23] However, the need for pharmacists' contribution in high-quality services, shown in this study, coincides with other studies of pharmacists' interventions in other ward settings.[14-19,22] Clinical services, provided by pharmacists, were shown to be important in the treatment of cancer patients, who are exposed to complex treatment with high-risk drugs.

Conclusions

This study showed the importance of the integration of pharmacists' clinical and technical knowledge in the dispensing of chemotherapy doses to provide high quality cancer services. Pharmacists' clinical activities in the dispensing of cancer drugs were shown to be essential for improving patient care and preventing major toxicity, and should be defined as a standard of care in guidelines, regulating the dispensing of chemotherapy doses of cancer drugs.

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case report

Digital ischemic events related to gemcitabine: Report of two cases and a systematic review

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Background. Gemcitabine is a potent cytotoxic agent used in the treatment of many solid tumours, sarcomas and lymphomas. Vascular toxicity and thrombotic events related to gemcitabine seem to be underreported.

Case report. We report two cases of gemcitabine related digital ischemic events.

Case 1. A 65-year-old man was given the first-line treatment with gemcitabine for the advanced adenocarcinoma of pancreas. After four weekly doses of gemcitabine (total dose 4000 mg/m^2) he presented with Raynaud's like phenomenon and ischemic fingertips necrosis in five digits of both hands. Symptoms resolved in all but one digit after stopping chemotherapy and treatment with iloprost trometamol infusion.

Case 2. A 77-year-old man, ex-smoker, was administered a combination of gemcitabine and cisplatin as the first-line treatment for the locally advanced bladder cancer. After 4 cycles of the treatment (total dose of gemcitabine 4000 mg/m^2) the patient suffered digital ischemia and necrosis on two digits of a right leg. Arteriography revealed preexisting peripheral arterial occlusive disease (PAOD) of both legs with very good peripheral collateral circulation and absent microcirculation of affected two digits. The gemcitabine treatment was stopped and the patient was treated with iloprost trometamol infusion and percutaneous transluminal angioplasty with dilatation of the right superficial femoral artery. Digital changes resolved without consequences. Severe thrombocytosis (platelet count 1211 x 10^9/L) might have also contributed to the ischemic digital event in the second case.

Conclusions. Digital ischemic events associated with gemcitabine chemotherapy seem to be more common in patients with tobacco-associated cancers, especially when used in combination with platinum salt. The treatment with gemcitabine in patients with evolving Raynaud's phenomenon and/or preexisting PAOD should be done with caution.

Key words: chemotherapy; gemcitabine vascular toxicity; digital ischemic events

Introduction

Gemcitabine is an important contemporary chemotherapeutic agent for the treatment of both solid tumours and lymphomas.[1] As a nucleoside analog structurally related to cytosine arabinoside, it interferes with the synthetic pathways of the tumour cell predominantly in the S phase of the cell cycle. It is a potent inhibitor of DNA synthesis and repair.[2]

First approved in 1996 for the treatment of unresectable pancreatic cancer, today gemcitabine is most commonly used in the therapy of pancreatic, ovarian, breast, non-small cell lung and bladder cancer, some sarcomas, cutaneous and peripheral T-cell lymphomas as well as in relapsed Hodgkin's lymphoma.[1] The use of this drug enables progress in the routine management of cancer patients.[3,4]

Gemcitabine is a drug with a favourable toxicity profile with myelosuppression, a flu-like syndrome, skin rash and radiation recall dermatitis being the most common side effects.[2]

As indications for its use in oncology have been expanding, some reports showed the possibility of its vascular side effects. Among them thrombotic microangiopathy[5], venous thrombembolism, acute arterial events (digital ischemia and necrosis, vasculitis), systemic capillary leak syndrome and

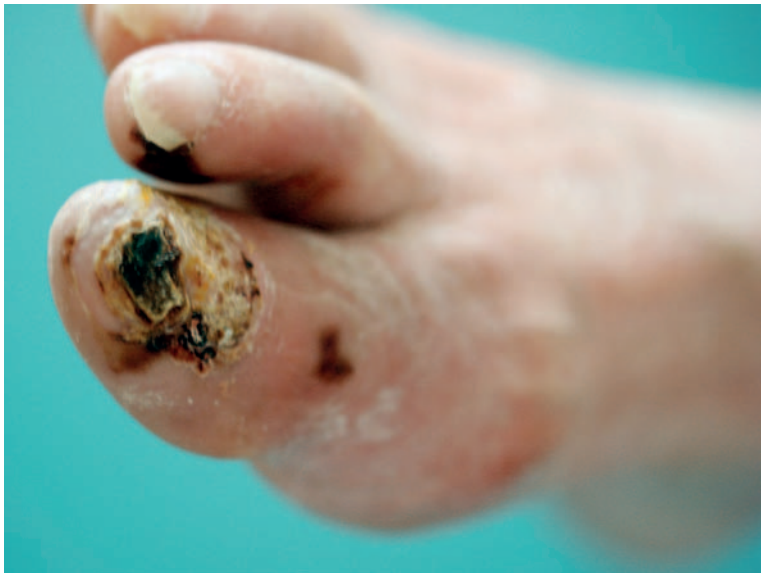

FIGURE 1. Ischemic necrosis on digits I and II of right foot after 4 cycles of chemotherapy with cisplatin and gemcitabine (Case 2).

reversible posterior leukoencephalopathy are reported.[1]

Digital ischemic events are rare in cancer patients. They are most frequently related to vascular disease due to hypercholesterolemia, arterial hypertension, diabetes or exposure to tobacco. They may also occur as a complication of connective tissue diseases, i.e. vasculitis with digital ischemic events.

In the present article we report two cases of digital ischemic events during the therapy with gemcitabine alone and in combination with cisplatin and review data in the literature regarding this rare side effect.

Case 1

A 65-year-old male was presented in March 2009 with primary metastatic adenocarcinoma of pancreas (metastases in retroperitoneal and cervical nodes). He had a history of nephrolythiasis ten years ago and 5 months lasting history of hydronephrosis of the left kidney of grade III, caused by enlarged retroperitoneal lymph nodes. At presentation he was overweight with grade I renal impairment (creatinine 129 μmol/L). He complained of pain in the upper abdomen. Tumour marker CA 19-9 was elevated (> 12 000 IU); platelet count was 376 x 10^9/L.

In March 16 2009 he started the treatment with gemcitabine monotherapy in a weekly dose 1000 mg/m^2. After 3 weekly doses he had less pain in the abdomen and tumour marker CA 19-9 halved (6163 IU). Platelet count was elevated (570 x 10^9/L). He complained of painful swelling in three digits of right hand and acrocyanosis. After the 4th dose of gemcitabine pain in digits increased and the patient was admitted to the local hospital. Raynaud's syndrome was suspected. Criteria for paraneoplastic microthrombosis, which was suspected, were not met. At the beginning the patient was treated with acetylsalicylic acid. No improvement was recorded. On the control visit in our institution (May 05 2009) the patient complained of severe pain in five digits of both hands. The examination showed dry fingertips necrosis. Radial and ulnar pulses were normal. The Doppler ultrasound of both arms showed normal macrocirculation. Digital plethismography showed an absent signal on digits I, II and IV of the right and digits III and V of the left hand. Gemcitabine induced vasculitis causing ischemia was suspected and gemcitabine treatment was stopped. The patient was treated with the prolonged infusion of a prostacycline analogue iloprost trometamol (20 mg/day for three weeks) and analgesic therapy with NSARD and opioids. Digital changes in all but one of affected digits resolved at the next visit in June 24 2009. Ischemic changes of distal phalange of digit V of the left hand required the amputation. The patient died in August 2009 due to the progressive disease.

Case 2

A 77- year-old male presented in May 06 2009 with a diagnosis of locally advanced bladder cancer (T4aN2M0). He was heavy a smoker in the past and had a history of gastric perforation due to peptic ulcer ten years ago. In February 2009 he was temporary on amiodarone medication due to paroxysm of atrial fibrillation. Otherwise he was in good physical condition. In April 2009 he underwent an attempt of radical cistoprostatectomy. Due to the local extension of the tumour only Bricker neovesica and biopsy of pelvic lymphnodes was performed. In May 2009 he was presented for induction chemotherapy and definitive radiotherapy afterwards. From May to August 2009 he received four cycles of chemotherapy with cisplatin and gemcitabine (cisplatin 75 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 every three weeks). None of the planned gemcitabine doses on day 8 was applied due to the infection. In August 8 2009 the patient presented with painful black spots on digits I and

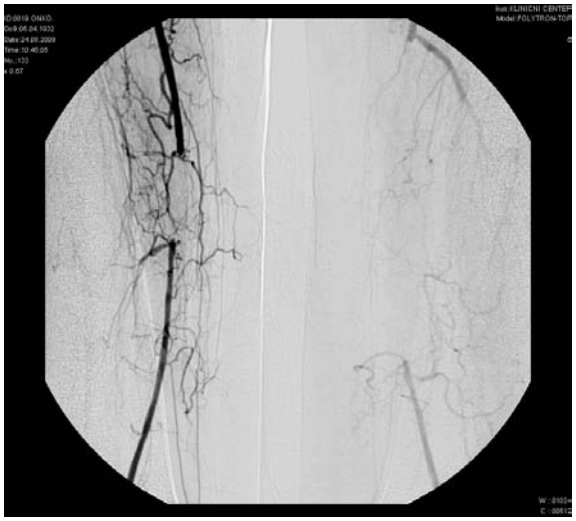

FIGURE 2. Pelvic arteriography showing occlusion of right superficial femoralis artery (AFS) in the length of 5 cm and of left AFS in length of 18 cm (Case 2).

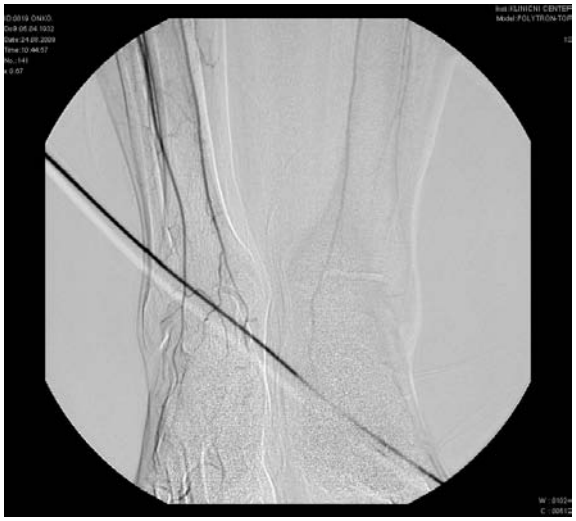

FIGURE 3. Arteriography showing impaired circulation of distal part of both legs in Case 2.

II of the right foot and subluxation of the thumbnail of the same foot. He underwent the ablation of the thumbnail. Ischemic changes in the thumb were suspected. In August 18 2009 the patient presented with the progressive painful fingertip necrosis on fingertips I and II of the right foot (Figure 1). The elevated platelet count was recorded (1211x10^9/L). He was sent to an angiologist. Doppler ultrasound showed severe peripheral arterial occlusive disease (PAOD) of both legs. Pelvic arteriography showed the occlusion of right superficial femoral artery (AFS) in the length of 5 cm and of left AFS in length of 18 cm, with very good collateral circulation on both sides and good transition of the both poplitheal arteries (Figure 2 and 3). The patient was treated with prolonged infusion of a prostacycline analogue - iloprost trometamol (20 mg/day for 7 days). A successful percutaneous transluminal angioplasty with dilatation of the right AFS was performed in September 1 2009. After this procedure the foot macrocirculation improved (warm skin of the right foot). Thereafter temporary wet necrosis and wound infection on digit II occurred, which healed until November 2 2009. The amputation of the affected digits was not required. Acetylsalicylic acid 100 mg/d was prescribed.

Discussion

Digital ischemic events in cancer patients are rare. However, in cancer patients with a history of heavy smoking, dislypidemia, arterial hypertension or diabetes, PAOD may already be presented at cancer diagnosis and may lead to ischemic events. In systemic sclerosis the impairment of microcirculation due to vasculitis and/or vasospasm can also cause a digital arterial obstruction.[6] Some anticancer agents (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone, doxorubicin, tamoxifen, cisplatin-gemcitabine combination) are implicated in thrombosis and thrombembolic events.[7] Therefore, in a patient with predisposing factors for the impaired microcirculation these anticancer agents may attribute to digital ischemic events.[6]

Among cases in the literature, Barcelo *et al.*[7] reported four cases of digital ischemic changes related to combination chemotherapy with gemcitabine plus cisplatin in patients treated for non-small cell lung cancer. In two of four cases a previously asymptomatic organic vascular lesion was aggravated while on chemotherapy with cisplatin and gemcitabine. Antiplatelet agent triflusal and vasoactive agent buflomedil were successful in resolving pain. One patient needed the additional leg amputation and two others thrombectomy.

Similarly, Venat-Bouvet *et al.*[8] described a patient with the acute onset of bilateral PAOD with necrosis of fingerpads which presented after the treatment with gemcitabine and platinum salt as a first line treatment for urothelial carcinoma of the bladder. The patient had a favourable outcome after chemotherapy withdrawal and infusion of iloprost trometamol, as in our Case 2. In our Case 2 cumulative dose of gemcitabine was only 4000 mg/m^2, in contrast to others (10000 mg/m^2, 14390 mg).[8,9]

Blaise *et al.*[9] reported two cases of digital ischemia. First was a female treated with gemcitabine as the second line for lymph-node metastatic squamous cell carcinoma of unknown origin. The second patient was treated for bladder carcinoma with gemcitabine and carboplatine. Both resolved after the interruption of gemcitabine and additional medical treatment.

Another case attributed to vascular toxicity of gemcitabine is reported by Holstein *et al.*[10] treated with platinum plus gemcitabine for advanced urothelial carcinoma. After the second cycle of chemotherapy the patient presented with digital ischemia. Digital amputation was avoided by sympathicolysis by bilateral blockade of brachial plexus and application of iloprost, heparin, corticosteroids and acetylsalicylic acid.

Patients with scleroderma are at high risk for developing digital infarction because of their underlying vascular disease and associated Raynaud's phenomenon. Clowse *et al.*[11] presented a patient with scleroderma who developed multiple ischemic digits after receiving combination chemotherapy of carboplatin plus gemcitabine for lung cancer. D'Allesandro *et al.*[12] reported a case with Raynaud type phenomenon, intermittent fever, digital necrosis and a fingertip gangrene after receiving two applications of gemcitabine for bladder cancer. The authors suggested caution in using such chemotherapy in subjects with autoimmune disorders (scleroderma, positive HEP-2 and cryoglobulin).[11,13]

Digital ischemic changes resolved in most cases after stopping the application of chemotherapy and the treatment with prostacyclin antagonists (iloprost or buflomedil). A more sophisticated treatment with sympathicolysis by bilateral thoracic block was reported to be efficient in digital ischemic event in scleroderma patient, where gangrenous ulcers occurred due to vaso-occlusive disease, which is a combination of occlusive vasculitis and symphatically-mediated vasospasm.[6] Sympathectomy and iloprost infusion were reported to be successful in the treatment of severe acral ischemia and necrotic lesions of several fingertips after receiving palliative chemotherapy with gemcitabine for inoperable squamous cell carcinoma of the tonsil.[14]

In our Case 1 the first signs of the impaired digital circulation (swollen and painful cold blue fingers) occurred after three weekly doses of gemcitabine therapy and worsened after the next weekly application of the same drug, therefore the causal relationship between gemcitabine and digital arterial ischemia seems very probable. The patient had no history or symptoms of preexsisting PAOD or connective tissue disease. The Raynaud's phenomenon can be a paraneoplastic manifestation in disseminated pancreatic cancer, but would already be present at presentation of disease and would probably improve with the effective anticancer therapy. The occurrence of digital ischemia was probably related to vascular toxicity of gemcitabine, as indicated by resolving microcirculation in 4 of 5 affected digits after the discontinuation of gemcitabine and the intervention with vasodilating agent iloprost.

In Case 2 after the cumulative dose of gemcitabine of 4000 mg/m^2 and cisplatin 300 mg/m^2 arterial ischemic necrosis on two digits of the right foot occurred. After a detailed investigation of the patient, severe preexisting PAOD of both legs with the very good collateral circulation was diagnosed. Gemcitabine may also be capable to cause endothelial damage and thrombocytosis.[1,2] The latter could also attribute to impaired microcirculation in our case (platelet count at 3rd cycle of chemotherapy 1211 x 10^9/L). At that time the patient was on fractionated heparin in prophylactic dosing. Instead of heparin, the antiagregation therapy with acetylsalicylic acid would be more appropriate in preventing digital arterial thrombosis. After the dilatation of the occluded segment of the main leg arterial vessel and vasodilatation effect of iloprost infusion both macro and microcirculation improved, respectively. Digital ischemic necroses resolved without durable consequences.

In both cases painful cold trophic skin changes were clinically suspicious of compromised arterial microcirculation, confirmed by absent plethysmographic signals. In Case 1 Doppler ultrasound showed good macrocirculation, which was severely impaired in Case 2, as already suggestive of PAOD by patient's long smoking history. Clinically absent pedal pulses and angiologic examination with arteriography could place angioplastic intervention before the initiation of chemotherapy with gemcitabine and cisplatin. A noninvasive evaluation of the leg arterial perfusion could be done by MRI enhanced angiography[15] and an invasive angiography being applied only in cases where an invasive procedure is indicated. The antiagregation therapy (acetylsalicylic acid 100 mg a day) in case of severe reactive thrombocytosis in cancer patients as well as in patients with cardiovascular factors is indicated and could prevent the development of digital ischemia in Case 2. Discontinuation of cisplatin plus gemcitabine and the intervention

with iloprost prometanol have been proven helpful in resolving microcirculation in both cases as documented by control plethysmography. Additionally calcium channel blockers and other vasodilatators were shown beneficial in resolving digital ischemia.[6,7,11]

Conclusions

Digital ischemic events associated with gemcitabine chemotherapy seem to be more common than previously thought, especially when used in combination with platinum salts and in patients with tobacco-associated cancers. In patients with known risk factors for PAOD, like dislypidemia, arterial hypertension, diabetes or tobacco smoking, and a history of intermittent claudication thorough the examination of peripheral pulses should be performed before the initiation of gemcitabine or platinum-gemcitabine doublet. In addition, if painful trophic digital changes develop while on therapy with gemcitabine, medical oncologists should refer the patient to an angiologist for the assessment of impaired micro or macrocirculation. In case of diagnosis of ischemic vascular event, discontinuation of gemcitabine and immediately therapy with prostacycline analogues should be initiated. The early diagnosis and the appropriate intervention improve not only the outcome of the ischemic vascular event but also the quality of life of the patient.

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case report

Ureteral metastasis as the first and sole manifestation of gastric cancer dissemination

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Background. Isolated ureteral metastasis from gastric cancer is extremely rare.

Case report. We describe a 50 year old man with a history of subtotal gastrectomy who presented 4 years later with an ureteral metastasis. He was asymptomatic and diagnostic tests were performed due to the elevated creatinine level disclosed incidentally. The partial resection of distal right ureter as well as the resection of the right ureterovesical junction was performed with the implantation of double J stent. Histopathology revealed a metastasis of the adenocarcinoma that matched perfectly a tumour specimen from the gastric cancer surgery. It was first and isolated manifestation of gastric cancer dissemination.

Conclusions. Although rare, the ureteral metastasis from gastric cancer can be the first, sole and asymptomatic manifestation of gastric cancer dissemination after a period of time.

Key words: ureteral metastasis; gastric cancer

Introduction

The so-called true metastasis to the ureter from gastric cancer occurring through lymphatic and/or blood vessels is found to be very rare.[1-3] There are also two other possibilities of the uretral obstruction: direct extension from the primary tumour, peritoneal deposit or lymph node metastasis of gastric cancer to the ureter – usually seen in the advanced cancer stage and autopsies[4]; and retroperitoneal fibrosis of the periureteral space induced by cancer cells.[5]

We report the case of a patient with ureteral metastasis as the first and sole manifestation of gastric cancer dissemination four years after he was first diagnosed with gastric cancer.

Case report

A 50-year old man was admitted to the Department of Urology, Clinical Hospital Centre Zagreb in June 2008, due to the hydronephrosis and raised creatinine blood level disclosed incidentally during his rehabilitation from brain stroke from which he had suffered in May 2008.

He had a history of subtotal gastrectomy for gastric cancer four years ago, stage T3N1M0. He received adjuvant chemo-radiotherapy. The patient had no pain at the admission. Routine blood test results were normal except elevated creatinine (192 μmol/L; normal range 63-107), urea (11.8 mmol/L; normal range 2.8-8.3) and C-reactive protein (CRP) (105 mg/L; normal range < 5) levels and mild anemia (hemoglobin 109 g/L; normal range 138-175). Urinalysis showed 3-7 erythrocytes and lot of leucocytes. Urine culture revealed Pseudomonas aeruginosa (10^3 CFU/ml). Multislice computed tomography (MSCT) disclosed atrophic left kidney and right hydronephrosis (Figure 1). Cystoscopy indicated normal bladder. Right retrograde pyelography (RP) was not done successfully because of the obstruction found at the 3 cm from the right

ureterovescial junction. Right antegrade pyelography showed hydrourether with contrast stop 4 cm below the right sacroilical joint.

On July 29, 2008, the partial resection of the distal right ureter as well as the resection of the right ureterovesical junction was performed with the implantation of a double J stent.

Histopathology revealed a metastasis of the adenocarcinoma. Fibromuscular and adipose tissue were infiltrated with tumorous tissue consisting of irregular glands lined with atypical colonic epithelial cells. No infiltration of a superficial transitional cell layer was found. The macroscopic observation of the periureteral region and of the retroperitoneal space did not reveal any pathology. Upon thorough comparison, tumour specimens of the resected ureter (year 2008) and gastric cancer (year 2004) were found to be completely identical (Figures 2a,b).

After the receipt of the histopathological report gastroscopy and colonoscopy were performed without any evidence of a tumour. Tumour markers were within the normal range: alpha- fetoprotein (AFP) (1.46 μg/L; normal range <13.4), carcinoembryonic antigen (CEA) (1.79 μg/L; normal range < 3.4), cancer antigen 19/9 (CA19-9) (16.93 kIU/L; normal range < 37), prostate-specific antigen (PSA) (1.44 μg/L, normal range < 4).

The patient was further transferred to the Department of Oncology for systemic chemotherapy. Unfortunately, he managed to receive only three cycles of chemotherapy (leucovorin, etoposide and fluorouracil) when presented with severe acute psychosis. Brain CT was without metastasis but his general and mental condition deteriorated and chemotherapy was never resumed. Finally, after several months his mental status gradually improved. Now, twelve months after the last chemotherapy he is well and without any signs of the disease.

Discussion

Ureteral metastasis from distant organs is a rare event.[1-3] The most common primary sites to metastasize to the ureter are breast, colon, prostate and cervix.[2,6] MacKenzie and Ratner[1] first proposed a criterion for the differentiation of a true metastasis from the direct extension of the tumour to the ureter. Later, Presman and Ehrlich[3] modified the criterion as follows: "the demonstration of malignant cells in a portion of the ureteral wall together with the absence of any neoplasm in adjacent tissue". Tumour in the ureteral wall without the in-

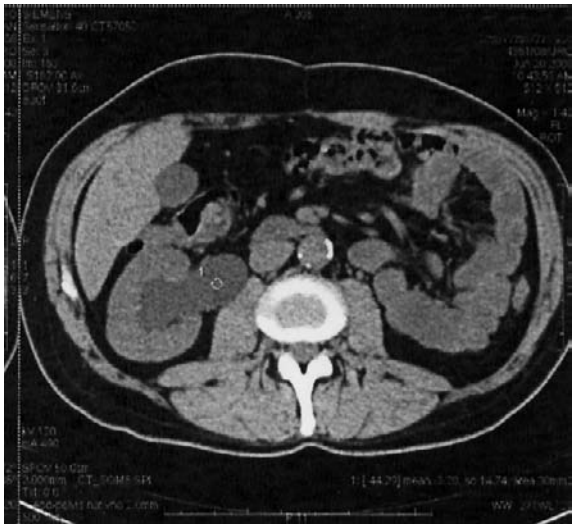
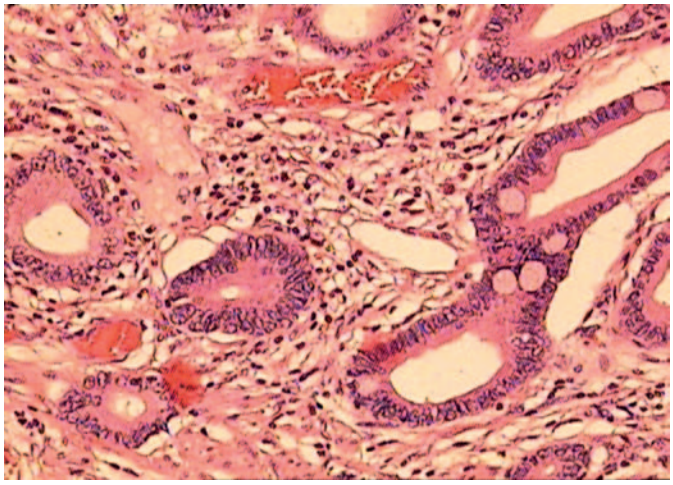
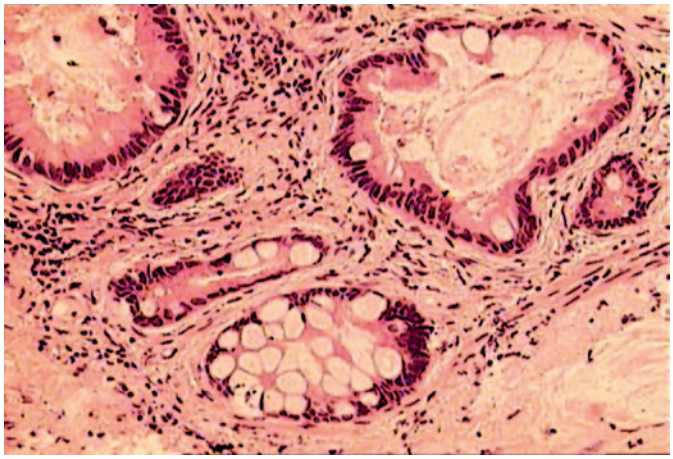


FIGURE 1. Multislice computed tomography (MSCT) - right hydronephrosis.



A

FIGURE 2A. Microscopic appearance of stomach cancer. Hematoxylin and eosin staining (20 x magnification).



B

FIGURE 2B. Microscopic appearance of the distal ureter cancer. Hematoxylin and eosin staining (20 x magnification).

vasion of the superficial transitional cell layer and the absence of any pathology in the periuretral and retroperitoneal space in our patient indicated the true uretral metastasis from gastric cancer.

Ureteral metastases from gastric cancer are extremely rare.[7,8] Schlagintweit[9] reported the first case of gastric cancer metastasizing to the ureter in 1911. Since then, cases have been occasionally reported. The majority of them were from Japanese population while reports from other populations were scarce.[10] Shimoyama *et al*.[10] reviewed 27 cases of the true ureteral metastasis from gastric cancer. The age of the patients ranged from 34 to 74 years with median age of 52 years. Eleven patients (41%) had previously undergone gastrectomy for gastric cancer. Our patient fitted the pattern.

Although rare on the whole, the ureteral metastasis from gastric cancer can be even the first manifestation of asymptomatic gastric cancer or the first and the sole manifestation of the gastric cancer dissemination after a period of time as in our case.[10-12] The prognosis is generally poor and the survival for more than 2 years has not been reported.[10]

There has been no report describing any effective therapy for this condition although there are some encouraging results with the multimodality treatment in another cases of patients with gastric cancer.[13] The new regimens including docetaxel or oxaliplatin could show some benefit in the future. However, the pathohystology accomplished with immunohystochemistry, the establishing of extend of disease and the performance status still remain the main prognostic factors. They also enable the appropriate choice of the treatment.[14]

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letter to the editor

Management of cetuximab-induced skin toxicity with the prophylactic use of topical vitamin K1 cream

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Cetuximab is an immunoglobulin G1 monoclonal antibody that binds to the extracellular domain of the epidermal growth factor receptor (EGFR) blocking ligand-induced auto-phosphorylation and subsequent receptor mediated signalling.[1,2] Cetuximab in combination with chemotherapy is effective in the treatment of EGFR-expressing tumors including metastatic colorectal cancer (mCRC).[2,3]

EGFR is strongly expressed in the keratinocytes, cells of eccrine and sebacceous glands and in the epithelium of hair follicles, and is important for normal skin development and function.[4] Blocking cutaneous EGFR signalling with EGFR inhibitors leads to a spectrum of skin reactions which occur in ≥80% of patients, the most common being acneiform rash which occurs most frequently on the head and neck regions and on the trunk. Other less frequent reactions include, pruritus, dry skin, desquamation, hypertrichosis, and paronychia.[1,2] Approximately 15% of cutaneous reactions are severe (≥ grade 3; US National Cancer Institute–Common Toxicity Criteria)[5], causing cetuximab therapy to be interrupted.[6]

We have investigated the prophylactic treatment of patients with a topically applied skin cream containing urea and 0.1% vitamin K1 (Renconval K1®) during cetuximab therapy. The aim of the study was to continue cetuximab without treatment delays or dose reductions, which may impact on tumour response rates.[7] Four patients with mCRC receiving first-line cetuximab in combination with chemotherapy, had applied vitamin K1 cream facially twice daily for 8 weeks from the first infusion of cetuximab. Patients were screened weekly

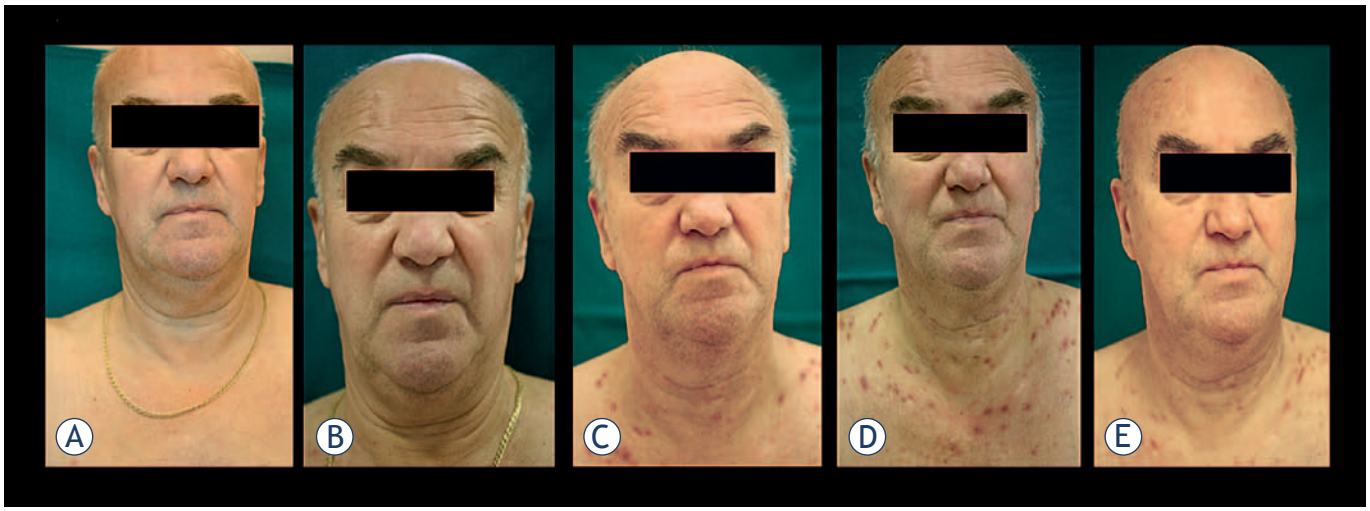

FIGURE 1. Cetuximab-related acneiform rash in a patient following prophylactic treatment with vitamin K1 cream.
Vitamin K1 cream was applied to patient B twice daily from the first infusion of cetuximab and first-line chemotherapy for mCRC. Photographs are shown taken during the assessment of aceniform rash at: a) first infusion of cetuximab; b), week 1; c) week 3, d) week 4 and e) week 8

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TABLE 1. Assessment of acenform rash in 4 patients treated with cetuximab in combination with chemotherapy and prophylactic vitamin K1 skin cream

Patient**	Weekly assessment score*								Tumour response
	1	2	3	4	5	6	7	8	
	F/T	F/T	F/T	F//T	F/T	F/T	F/T	F/T	
A	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	SD
B	0/+	0/+++	0/++	0/++	0/++	0/++	0/+	0/+	CR
C	0/++	+/+++	+/+++	0/++	0/++	0/++	0/+	0/+	PR
D	0/+	0/++	0/++	0/+	0/+	0/+	0/+	0/+	PR

*Scoring system 0=no rash; += mild rash, ++= moderate rash and +++= severe rash

**Three males and one female, average age: 61.75 years.

F= face; T= trunk; SD, stable disease; CR, complete response; PR, partial response

and photographs taken. The study was performed in accordance with the Declaration of Helsinki (5th revision, October 2000) of the World Medical Association[8] and approved by the National Medical Ethics Committee of the Republic of Slovenia. Patients provided written informed consent.

During treatment, no topical or oral antibiotics were prescribed and other moisturizers were not needed. Only one patient was judged to have developed mild facial papules and all four patients developed acneiform eruptions on the trunk ranging from mild to severe. The grade of acneiform rash was reduced where vitamin K1 cream was applied as prophylaxis (Table 1 and Figure 1).

At the end of cetuximab treatment one complete response, one stable disease and two partial responses were recorded.

Vitamin K activates EGFR signalling; preclinical studies have shown that 0.1–0.5 mM vitamin K3 completely abrogated EGFR inhibition *in vitro* and was associated with upregulation of phosphorylated EGFR in the skin when used in topically applied cream.[9,10] In a study of 30 patients treated with Reconval K1® on the first appearance of acneiform rash, we previously reported a median time to improvement of 8 days, and down-staging of rash by ≥1 grade after 18 days. No cetuximab dose reductions or treatment delays were required in patients with grade ≤2 cutaneous toxicity and no toxicities associated with Reconval K1® were reported.[7,11]

In the present study we investigated the prophylactic use of vitamin K1 cream to the face in comparison with the trunk, which received no treatment. Whilst curative treatment has already been reported to be effective[7], prophylactic treatment is potentially more effective. No cetuximab dose reductions or treatment delays were required. The topical use of vitamin K1 cream for preventing or reducing cetuximab-related acneiform rash appears to be promising.

It remains very important to treat skin reactions related to EGFR inhibitors promptly to ensure a better patient quality of life without dose reduction or drug discontinuation. We conclude that Reconval K1® has potential for prophylactic use in the treatment of cetuximab-related skin toxicity, but that further studies are required to evaluate the impact of its use on tumor response rates and patient quality of life.

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Citološka preiskava urina in izpirka sečnega mehurja pri ugotavljanju urotelijskega karcinoma: standardni test in nove možnosti

Strojan Fležar M

Izhodišča. Svetlobnomikroskopska ocena celične morfologije na preparatih, pripravljenih iz odluščenih celic v vzorcih urina in izpirka sečnega mehurja, omogoča osnovno in prvo diagnostiko malignomov sečnega mehurja pa tudi ostalih delov urinarnega trakta. S citopatološko preiskavo odkrivamo tudi ponovitve bolezni ob kontrolnih pregledih pri bolnikih, ki so že bili zdravljeni zaradi karcinoma sečnega mehurja ali nov primarni tumor.

Zaključki. Značilni celični in jedrni znaki malignosti omogočajo zanesljivo citopatološko diagnostiko invazijskega urotelijskega karcinoma in *in situ* karcinoma ter večine papilarnih urotelijskih karcinomov visokega gradusa. Metoda ima nizko občutljivost in je nezanesljiva za diagnostiko papilarnih urotelijskih neoplazem nizkega gradusa, ker so celični in jedrni znaki malignosti pri teh neoplazmah slabo izraženi. Da bi izboljšali diagnostiko karcinoma sečnega mehurja iz urina, so razvili različne nove označevalce. Med najnovejšimi je test UroVysion™, to je metoda fluorescenčne in situ hibridizacije, s katero ugotavljamo specifične citogenetske spremembe, značilne za urotelijske karcinome.

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Radiološki znaki osteonekroze čeljustnic povzročene z bisfosfonati

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Izhodišča. Bisfosfonati so zdravila, ki jih uporabljamo za zdravljenje osteolitičnih metastaz, plazmocitoma, z malignimi obolenji povzročene hiperkalcemije, osteoporoze in Pagetove bolezni. Uporaba bisfosfonatov lahko povzroči osteonekrozo čeljustnic. Namen naše študije je predstaviti radiološke znake osteonekroze čeljustnic povzročene z bisfosfonati.

Bolniki in metode. Pri enajstih bolnikih z bolečnino v čeljusti slabšim celjenjem na mestu ekstrakcije zoba, gnojnim iztokom in otekanjem v področju mehkih tkiv smo opravili CT in MRI preiskavo obeh čeljustnic s kontrastnim sredstvom. Povprečni čas zdravljenja z bisfosfonati je bil 28 mesecev. Vsi bolniki so bili zdravljeni kirurško z odvzemom histološkega vzorca, v katerem je bila dokazana osteonekroza.

Rezultati. CT preiskava je pokazala osteolitične in osteosklerotične spremembe z erozijami kortikalne plasti čeljustnic pri vseh bolnikih, vključenih v našo študijo. Na MRI preiskavi s kontrastnim sredstvom smo osteonekrozo videli kot neostro omejeno spremembo z zmanjšanim signalom tako na T1 kot T2 obteženi sekvenci. Pri vseh bolnikih smo na MRI preiskavi opazovali oteklino mehkih tkiv s patološkim obarvanjem po kontrastnem sredstvu v področju bukcinatornega in mastikatornega prostora ter vnetno spremenjene bezgavke submandibularne in jugularne digastrične verige

Zaključki. Pri osteonekrozi čeljustnic povzročeni z bisfosfonati smo s slikovno preiskovalnimi metodami prikazali različne radiološke znake, s katerimi bolezen lahko prepoznamo, zamejimo in jo spremljamo. Noben od radioloških znakov pa ni značilen samo za to vrsto osteonekroze.

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Ocenjevanje perianalnih fistul z magnetno resonanco

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Izhodišča. Kot fistulo opredeljujemo patološko povezavo med dvema epitelialnima površinama. Parksova klasifikacija ima veliko praktično vrednost in fistule deli na intersfinkterične, transsfinkterične, suprasfinkterične in ekstrasfinkterične. Etiologija perianalnih fistul je največkrat povezana z vnetjem analnih žlez pri Crohnovi bolezni, tuberkulozi, medeničnih okužbah ter z medeničnimi malignimi tumorji in radioterapijo. Fistule lahko slikovno prikažemo z rentgensko fistulografijo, fistulografijo z računalniško tomografijo (CT) ali pa z magnetno resonanco (MR) medeničnih organov.

Bolniki in metode. V prospektivno raziskavo smo vključili 24 bolnikov, ki so imeli perirektalno fistulo. Pri vseh smo naredili rentgensko fistulografijo, fistulografijo s CT preiskavo in preiskavo medeničnih organov z MR. Statistično smo analizirali natančnost vsake preiskave glede na spol bonikov in etiologijo fistul.

Rezultati. Ugotovili smo 29,16% transsfinkteričnih fistul, 25% intersfinkteričnih, 25% rekto-vaginalnih, 12,5% ekstrasfinkteričnih in 8,33% suprasfinkteričnih. Absces smo prikazali pri 16,6% bolnikov. Najpogostejši vzrok perianalnih fistul je bila Crohnova bolezen (37,5%), kjer je bila natančnost opredelitve fistul z MR 100%, s CT 11% in s rentgensko preiskavo 0%. Ulcerozni kolitis je bil drugi najpogostejši vzrok za nastanek fistul (20,9%), kjer je bila natančnost opredelitve fistul z MR 100%, s CT 80% in s rentgensko preiskavo 0%. Ostale vzroke nastanka fistul smo našli pri 41,6% bolnikov.

Zaključki. MR je zanesljiva diagnostična metoda za opredelitev perirektalnih fistul in nam lahko znatno pomaga v predoperativni pripravi za uspešen kirurški poseg. Na ta način lahko zmanjšamo število ponovitev bolezni. Prednost je tudi, da lahko brez uporabe kontrastnega sredstva natančno prikažemo fistulo in absces.

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Mamografsko okultni duktalni rak in situ (DCIS), visokega gradusa kot drugi primarni rak dojke, odkrit z magnetno resonanco – prikaz primera

Zebič-Šinkovec M, Kadivec M, Podobnik G, Škof E, Snoj M

Izhodišča. Najpogostejši drugi primarni rak dojke pri bolnicah, ki so že imele rak dojke, je rak kontralateralne dojke. Ko ga odkrijemo, je največkrat že invazivne oblike. Skoraj vsi invazivni raki dojke se razvijejo iz in situ karcinoma. Senzitivnost magnetne resonance za DCIS je precej višja od mamografije.

Prikaz primera. Bolnica je bila pred 10 leti že operirana zaradi raka dojke. Naredili so ohranitveno operacijo, histološko pa je bil ugotovljen medularni karcinom dojke. Po 10 letih smo v drugi dojki odkrili DCIS visokega nuklearnega gradusa. DCIS je bil mamografsko neviden (okulten), odkrit z magnetno resonanco in potrjen z biopsijo pod kontrolo magnetne resonance.

Zaključki. Preiskava dojk z magnetno resonanco bi lahko postala sestavni del preiskav v sledenju bolnic z diagnozo rak dojke.

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Učinek kakovosti odgovora na zdravljenje in zgodnje uvedbe rituksimaba na celokupno preživetje in preživetje brez ponovitve bolezni pri bolnikih z B-celičnim limfomom

Horvat M, Jezeršek Novaković B

Izhodišča. Uvedba rituksimaba v zdravljenje bolnikov z ne-Hodgkinovimi limfomi je prispevala k boljšim rezultatom zdravljenja – izboljšal se je odgovor na zdravljenje, podaljšalo trajanje remisij in celokupno preživetje bolnikov z B-celičnimi limfomi. Le malo raziskav pa je poskušalo razjasniti, ali boljši odgovor na zdravljenje (t.j. popolni odgovor) in zgodnja uvedba rituksimaba v zdravljenje prispevata tudi k daljšemu preživetju bolnikov. Namen naše retrospektivne raziskave je bil ugotoviti morebitno povezavo tako med kakovostjo odgovora na zdravljenje kot linijo zdravljenja z rituksimabom ter celokupnim preživetjem in preživetjem brez ponovitve bolezni .

Bolniki in metode. V raziskavi smo preučevali rezultate zdravljenja bolnikov z različnimi histološkimi tipi B-celičnih limfomov, ki so bili v obdobju od 2003 do 2007 zdravljeni na Onkološkem inštitutu Ljubljana s kombinacijo rituksimaba in kemoterapije. V raziskavo smo vključili le bolnike, ki so imeli pred uvedbo zdravljenja opravljeno določitev jakosti ekspresije CD20 s kvantitativno pretočnocitometrično metodo. Celokupno preživetje in preživetje brez ponovitve bolezni smo določili po Kaplan-Meierjevi metodi.

Rezultati. V raziskavo smo vključili 114 bolnikov. Bolniki, ki so po zdravljenju z rituksimabom dosegli popolni odgovor, so imeli statistično značilno daljše celokupno preživetje kot tisti, ki so dosegli le delni odgovor na zdravljenje (razmerje tveganj [HR] 0,34; 95% interval zaupanja [CI] 0,05 do 0,91; P = 0,0375) ali tisti, pri katerih se je bolezen stabilizirala (HR 0,11; 95% CI 0,0002 do 0,033; P < 0,0001) ali napredovala (HR 0,09; 95% CI 0,003 do 0,03; P < 0,0001). Bolniki, ki so dosegli popolni odgovor (CR; n = 70; 61,4%), so imeli tudi statistično značilno daljše preživetje brez ponovitve bolezni (razmerje tveganj [HR], 0,26; 95% CI, 0,021 do 0,538, P = 0,0068) kot tisti, ki so dosegli le delni odgovor (PR; n = 17; 14,9%). Bolniki, ki so prejeli rituksimab v sklopu prvega reda zdravljenja (n = 50; 43,9%), so imeli statistično značilno daljše celokupno preživetje kot tisti, ki so bili zdravljeni z rituksimabom ob prvi (HR 0,27; 95% CI 0,106 do 0,645; P = 0,0036) ali drugi ponovitvi bolezni (HR 0,22; 95% CI 0,078 do 0,5; P = 0,0006). Tudi preživetje brez ponovitve bolezni je bilo pri bolnikih, ki so bili z rituksimabom zdravljeni v prvem redu (n = 46; 52,9%), statistično značilno daljše (HR 0,32; 95% CI 0,088 do 0,9; P = 0,0325) kot pri bolnikih, ki so rituksimab prejeli v sklopu zdravljenja prve ponovitve bolezni (n = 25; 28,7%).

Zaključki. Naši rezultati kažejo, da boljši odgovor na zdravljenje verjetno prispeva k boljšemu celokupnemu preživetju in preživetju brez ponovitve bolezni pri bolnikih z B-celičnimi limfomi. Tudi zgodnja uvedba rituksimaba v zdravljenje (t.j. prvolinijsko zdravljenje) verjetno izboljša celokupno preživetje. Ko se torej odločamo o zdravljenju bolnikov z B-celičnimi limfomi, je smiselna uvedba rituksimaba v prvem redu zdravljenja v kombinaciji, pri kateri pričakujemo največji delež popolnih odgovorov na zdravljenje.

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Drugi primarni rak pri bolnikih z želodčnim rakom

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Izhodišča. Pri bolnikih z želodčnim rakom je večja nevarnost, da zbolijo za drugim rakom kot pri ljudeh v splošni populaciji. Namen raziskave je bil proučiti kliničnopatološke značilnosti teh drugih primarnih rakov.

Bolniki in metode. V retrospektivni klinični raziskavi smo analizirali bolnike, ki smo jih zdravili od leta 1995 do 2005 zaradi primarnega želodčnega raka. Upoštevali smo merila Warrena in Gatesa za druge (sekundarne) primarne rake.

Rezultati. 9 od 112 bolnikov z želodčnim rakom je imelo drugi primarni rak. 7 je bilo moških in 2 ženski; 6 jih je imelo sinhroni in 3 metahroni drug primarni rak. Bolniki so bili stari od 53 do 78 let, srednja starost je bila 61 ± 8,3 let. Najbolj pogosto smo ugotovili rak debelega črevesa in danke (33%), rak zgornjih dihalnih poti (22%) in rak sečil (22%).

Zaključki. V raziskavi smo ugotovili, da je incidenca drugega primarnega pri bolnikih z želodčnim rakom 8%. Priporočamo skrbne pre- in postoperativne preiskave za odkrivanje drugega primarnega raka in preiskave za opredelitev razširjenosti želodčnega raka. Ker je pri bolnikih z rakom želodca rak debelega črevesa in danke najbolj pogost drugi primarni rak, svetujemo ob sledenju bolnika usmerjene preiskave, kot sta n.pr. abdominopelvični CT in kolonoskopija.

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Limfedem po zdravljenju raka v Sloveniji: pogosto spregledana posledica?

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Izhodišča. Sekundarni limfedem je pogosta, velikokrat boleča posledica zdravljenja raka, ki zmanjšuje kakovost bolnikovega življenja, ovira gibanje in predstavlja tveganje za razvoj zapletov, kot so okužbe in maligne bolezni. Pri zdravljenju limfedema je bistvenega pomena čim prejšnje ukrepanje, še preden pride do nepopravljivih sprememb v tkivu.

Bolniki in metode. Opravili smo retrospektivno raziskavo bolnikov z limfedemom, ki smo jih od januarja 2002 do junija 2010 zdravili na Dermatovenerološki kliniki Univerzitetnega kliničnega centra Ljubljana. Zbrali smo demografske podatke bolnikov ter podatke o vrsti raka, vrsti in stadiju limfedema ter času do prve terapije limfedema. S pomočjo osnovnih statističnih metod smo primerjali število obravnavanih bolnikov z limfedemom po zdravljenju melanoma, raka dojke in raka maternice/maternicnega vratu, in število pričakovanih slovenskih bolnikov z limfedemom, izračunano na osnovi objavljenih poročil o incidenci.

Rezultati. V obdobju 8,5 let smo obravnavali 543 bolnikov (432 žensk, 112 moških) z limfedemom. Rezultati kažejo, da verjetno številnih slovenskih bolnikov s sekundarnim limfedemom po zdravljenju raka ne prepoznamo in jih ne zdravimo ali pa premalo zdravimo. Pri večini naših bolnikov smo začeli zdraviti limfedem pozno, povprečno šele po 3,6 letih po začetku limfedema.

Zaključki. Da bi preprečili zapoznelo diagnozo in obravnavo limfedema po zdravljenju raka ter posledične zaplete, mora zdravnik v času spremljanja onkološkega bolnika aktivno iskati znake in simptome limfedema. Bolnike s težavami mora takoj zdraviti ali napotiti na zdravljenje.

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Ocena kliničnih intervencij farmacevtov pri pripravi protitumorskih zdravil

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Izhodišča. Protitumorska zdravila uvrščamo med učinkovine z velikim tveganjem. Napake v njihovem predpisovanju, pripravi in aplikaciji imajo lahko resne posledice za bolnikovo zdravje, vključno z možnim smrtnim izidom. Kljub temu da je multidisciplinarno delo in sodelovanje farmacevtov v onkološki dejavnosti že uveljavljeno kot eden izmed načinov za zmanjševanje zgoraj omenjenega tveganja, je doprinos kliničnih farmacevtov slabo raziskan. Namen prispevka je analizirati klinične intervencije farmacevtov pri pripravi protitumorskih zdravil ter oceniti njihov prispevek k izboljšanju zdravljenja onkoloških bolnikov.

Metode. Klinične intervencije farmacevtov smo beležili v enoti za pripravo protitumorskih zdravil v terciarnem onkološkem centru v Londonu. Farmacevte smo opazovali med dvema procesoma: med pregledom ustreznosti predpisane terapije ter pri izdaji pripravljenega zdravila. Klinični pomen zabeleženih intervencij smo določili na osnovi soglasja, ki smo ga dosegli po strokovni farmacevtski razpravi.

Rezultati. Farmacevte smo opazovali pri 130 pregledih naročil ali izdaji zdravil. Zabeležili smo 21 intervencij. Problemi, ki so bili povezani z vsebinama »zdravilo in terapija« (38%) in »odmerek, režim odmerjanja in trajanje« (19%), ter problemi »administrativne narave« (22%) so najbolj pogosto zahtevali farmacevtovo intervencijo in kažejo na področja, kjer so potrebne izboljšave. Predlagane intervencije so upoštevali v 86%. Ocenili smo, da je bilo 48% intervencij zelo pomembnih za bolnikovo zdravljenje.

Zaključki. S svojimi intervencijami klinični farmacevti pripomorejo k boljši obravnavi onkoloških bolnikov. Za zagotavljanje visoke kakovosti onkološke dejavnosti morajo biti v zdravljenje s protitumorskimi zdravili vključene tudi farmacevtove klinične storitve.

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Ishemija prstov v povezavi z zdravljenjem z gemcitabinom: dva primera in pregled literature

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Izhodišča. Gemcitabin je učinkovit citostatik, ki ga uporabljamo za zdravljenje številnih solidnih tumorjev pa tudi sarkomov in limfomov. Ob množični uporabi gemcitabina je vedno več tudi poročil o žilnih in trombotičnih zapletih.

Prikaz primerov. Prestavljamo dva primera ishemije prstov, ki sta najverjetneje povezana z gemcitabinom.

Prvi bolnik je bil star 65 let in smo ga zdravili z gemcitabinom zaradi napredovalega karcinoma pankreasa. Po štirih tedenskih aplikacijah gemcitabina (skupno 4000 mg/m^2) so se mu na prstih rok pojavile spremembe podobne Raynaudovemu fenomenu. Po ukinitvi gemcitabina in infuziji iloprost trometamola so spremembe izzvenele brez posledic na vseh prstih razen enem.

Drugi bolnik je bil star 77 let in je bil bivši kadilec. Zaradi napredovalega karcinoma sečnega mehurja smo se odločili za prvo zdravljenje s kombinirano kemoterapijo gemcitabina in cisplatina. Po 4 krogih kemoterapije (skupni odmerek gemcitabina 4000 mg/m^2) je bolnik utrpel ishemijo in nekrozo dveh prstov na desni nogi. Arteriografija je pokazala preeksistentno periferno arterijsko okluzivno bolezen obeh nog z zelo dobro periferno kolateralno cirkulacijo, a odsotno mikrocirkulacijo na prizadetih dveh prstih. Zdravljenje s kemoterapijo smo prekinili. Nato smo bolnika zdravili z infuzijo iloprost trometamola in perkutano transluminalno angioplastiko z dilatacijo desne superficialne femoralne arterije. Spremembe na prstih so povsem izginile. Huda trombocitoza (število trombocitov 1211 x 10^9/L) je lahko dodatno prispevala k ishemičnim spremembam na prstih.

Zaključki. Ishemični dogodki prstov, ki so povezani s kemoterapijo z gemcitabinom, so pogostejši pri bolnikih z raki, ki jih povezujemo s kajenjem. Pogostejši so, kadar uporabljamo kombinacijo gemcitabina s platino. Pri bolnikih z razvijajočim se Raynaudovim fenomenom in preeksistentno periferno arterijsko okluzivno boleznijo moramo biti pri uporabi gemcitabina pozorni na razvoj ishemije prstov.

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Ureteralni zasevek kot prvi in edini znak razširitve želodčnega raka

Bišof V, Juretić A, Pasini J, Ćorić M, Grgić M, Gamulin M, Rakušić Z, Krajina Z, Bašić-Koretić M, Mišir A

Izhodišča. Posamični ureteralni zasevek, ki ga povzroči želodčni rak, je izredno redek.

Prikaz primera. Predstavljamo 50-letnega bolnika, ki so mu pred 4 leti subtotalno odstranili želodec zaradi želodčnega raka, nato pa se je pojavil posamični ureteralni zasevek. Bolnik je bil brez simptomov, dodatne preiskave pa smo naredili, ker je imel ob rutinskem pregledu povišan kreatinin. Naredili smo delno resekcijo distalnega desnega ureterja in resekcijo ureterovesikalnega stika ter vstavili opornico v obliki črke *J*. Histopatološki pregled je potrdil adenokarcinom, ki se je ujemal s histopatološko sliko narejeno ob operaciji želodca. To je bil prvi in edini zasevek želodčnega raka.

Zaključki. Čeprav redko je lahko ureteralni zasevek prvi in edini znak razširitve želodčnega raka. Pojavi se lahko po daljšem času po prvem zdravljenju.

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.*

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 2 – 4, 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

Authors Index 2010

Subject Index 2010

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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the final quarter of 2010

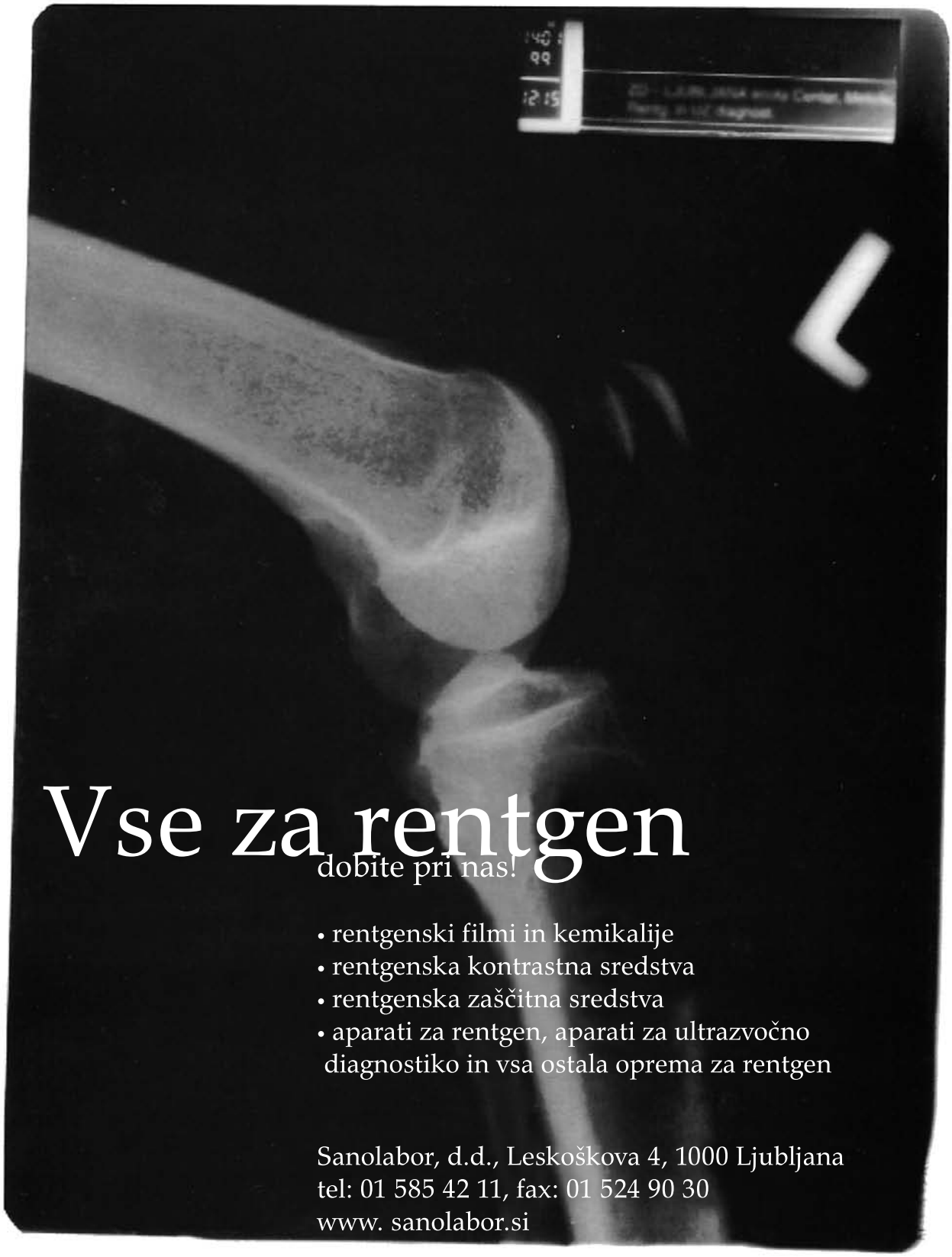
The Dr. J. Cholewa Foundation for Cancer Research and Education is a non-profit, non-government and non-political association of individuals, institutions and organisations. In the main part of its activities it supports various initiatives in cancer research, cancer prevention and cancer education among medical and other professionals, and in general population.

The Foundation distributed a number of grants to applicants wishing to extend existing or gain new knowledge in various fields of oncology. It also helped a number of professional and other associations, connected in various ways with advanced cancer research, to organise scientific and other meetings or symposia of specific interest. The support was also given to Slovenian Cancer Association for publication of various brochures and booklets. Among the activities mentioned above, the Foundation also continues to support the 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 website.

One of the goals of the of Dr. J. Cholewa Foundation for Cancer Research and Education is also to make modern and up to date treatments available to Slovenian patients as soon as possible; the easiest way to achieve this goal is in Foundation's opinion the spread of knowledge about advancements in various fields of oncology. Within its possibilities, the Foundation supports the implementation of all advances in cancer therapy and education into everyday hospital, ambulatory and health promotion practice. Hopefully, the results of cancer research will thus find their way into the practical application across Slovenia in as short a period as possible.

The Foundation hopes to successfully continue with its activities in the last few remaining months of 2010, leading to greater application of the latest cancer diagnostic, therapy and education methods and knowledge to research, clinical and public environment in Slovenia.

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



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Izredno učinkovito zdravljenje prvega reda pri nedrobnoceličnem pljučnem raku z mutacijo EGFR

Iressa je prva in edina tarčna monoterapija, ki dokazano podaljša preživetje brez napredovanja bolezni v primerjavi z dvojno kemoterapijo kot zdravljenje prvega reda pri bolnikih z napredovalim nedrobnoceličnim pljučnim rakom z mutacijo EGFR. [1]

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

1. Povzetek glavih značilnosti zdravila Iressa (gefitinib). Junij 2009.

Sestava: Filmsko obložene tablete vsebujejo 250 mg gefitiniba. **Indikacije:** zdravljenje odraslih bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim rakom z aktivacijskimi mutacijami EGFR-TK **Odmerjanje in način uporabe:** Zdravljenje z gefitinibom mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil proti raku. Priporočeno odmerjanje zdravila IRESSA je ena 250-mg tableta enkrat na dan. Tableto je mogoče vzeti s hrano ali brez nje, vsak dan ob približno istem času. **Kontraindikacije:** preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov, dojenje **Opozorila in previdnostni ukrepi:** Pri 1,3 % bolnikov, ki so dobivali gefitinib, so opažali intersticijsko bolezen pljuč (IBP). Ta se lahko pojavi akutno in je bila v nekaterih primerih smrtna. Če se bolniku poslabšajo dihalni simptomi, npr. dispneja, kašelj in zvišana telesna temperatura, morate zdravljenje z zdravilom IRESSA prekiniti in bolnika takoj preiskati. če je potrjena IBP, morate terapijo z zdravilom IRESSA končati in bolnika ustrezno zdraviti. čeprav so bile nepravilnosti testov jetrnih funkcij pogoste, so jih redko zabeležili kot hepatitis. Zato so priporočljive redne kontrole delovanja jeter. V primeru blagih do zmernih sprememb v delovanju jeter je treba zdravilo IRESSA uporabljati previdno. Če so spremembe hude, pride v poštev prekinitev zdravljenja. Zdravilo IRESSA vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze2galaktoze ne smejo jemati tega zdravila. Bolnikom naročite, da morajo takoj poiskati zdravniško pomoč, če se jim pojavijo kakršnikoli očesni simptomi, huda ali dolgotrajna driska, navzea, bruhanje ali anoreksija, ker lahko vse te posredno povzročijo dehidracijo. **Medsebojno delovanje zdravile:** Induktorji CYP3A4 lahko povečajo presnovo gefitiniba in zmanjšajo njegovo koncentracijo v plazmi. Zato lahko sočasna uporaba induktorjev CYP3A4 (npr. fenitoina, karbamazepina, rifampicina, barbituratov ali zeliščnih pripravkov, ki vsebujejo šentjanževko/Hypericum perforatum) zmanjša učinkovitost zdravljenja in se ji je treba izogniti. Pri posameznih bolnikih, ki imajo genotip slabih metabolizatorjev s CYP2D6, lahko zdravljenje z močnim zaviralcem CYP3A4 poveča koncentracijo gefitiniba v plazmi. Na začetku zdravljenja z zaviralcem CYP3A4 je treba bolnike natančno kontrolirati glede neželenih učinkov gefitiniba. Pri nekaterih bolnikih, ki so jemali varfarin skupaj z gefitinibom, so se pojavili zvišanje internacionalnega normaliziranega razmerja (INR) in/ali krvavitve. Bolnike, ki sočasno jemljejo varfarin in gefitinib, morate redno kontrolirati glede sprememb protrombinskega časa (PČ) ali INR. Zdravila, ki občutno in dolgotrajno zvišajo pH v želodcu npr. zaviralci protonske črpalke in antagonisti H2, lahko zmanjšajo biološko uporabnost gefitiniba in njegovo koncentracijo v plazmi in tako zmanjšajo učinkovitost. Redno jemanje antacidov, uporabljenih blizu časa jemanja zdravila IRESSA, ima lahko podoben učinek. **Neželeni učinki:** V kumulativnem naboru podatkov kliničnih preskušanj III. faze so bili najpogosteje opisani neželeni učinki, ki so se pojavili pri več kot 20 % bolnikov, driska in kožne reakcije (vključno z izpuščajem, aknami, suho kožo in srbenjem). Neželeni učinki se ponavadi pojavijo prvi mesec zdravljenja in so praviloma reverzibilni. Ostali pogostejši neželeni učinki so: anoreksija, konjunktivitis, blefaritis in suho oko, krvavitev, npr. epistaksa in hematurija, intersticijska bolezen pljuč (1,3 %), navzea, bruhanje, stomatitis, dehidracija, suha usta, nepravilnosti testov jetrnih funkcij, bolezni nohtov, alopecija, asimptomatično laboratorijsko zvišanje kreatinina v krvi, proteinurija, astenija, pireksija. **Vrsta in vsebina ovojnine:** škatla s 30 tabletami po 250 mg gefitiniba **Način izdajanja zdravila:** samo na recept **Datum priprave besedila:** junij 2009 **Imetnik dovoljenja za promet:** AstraZeneca AB, S-151 85, Sodertalje, Švedska Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila. **Dodatne informacije so na voljo pri:** AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, 1000 Ljubljana, telefon: 01/51 35 600.

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- absolutno število nevtrofilcev (ANC – Absolute Neutrophil Count) ≥ 1,5 x 109/l;
- število trombocitov ≥ 100 x 109/l;
- skupna merila toksičnosti (SMT) za nehematološko toksičnost ≤ 1. stopnje (z izjemo alopecije, navzee in bruhanja).

Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko.

Faza monoterapije Štiri tedne po zaključku faze sočasnega zdravljenja s TMZ in RT naj bolnik jemlje TMZ do 6 ciklov monoterapije. V 1. ciklu (monoterapije) je odmerek zdravila 150 mg/m2 enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m2, če je SMT za nehematološko toksičnost za 1. cikel stopnje ≤ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (ANC) ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Če odmerka niste povečali v 2. ciklu, ga v naslednjih ciklih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m2 na dan v prvih 5 dneh vsakega naslednjega cikla, razen če nastopi toksičnost. Zmanjšanje odmerka in ukinitev zdravila med fazo monoterapije opravite, kot je opisano v preglednicah 2 in 3. Med zdravljenjem morate 22. dan pregledati celotno krvno sliko (21 dni po prvem odmerku TMZ). **Odrasli in pediatrični bolniki, stari 3 leta ali več, s ponavljajočim se ali napredujočim malignim gliomom:**Posamezen cikel zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo TMZ v odmerku 200 mg/m2 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/m2 enkrat na dan, v drugem ciklu pa se poveča na 200 mg/m2 enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Preobčutljivost za dakarbazin (DTIC). **Posebna opozorila in previdnostni ukrepi: Pljučnica, ki jo povzroča Pneumocystis carinii** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da pri bolnikih, ki so sočasno prejemali TMZ in RT, obstaja še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s Pneumocystis carinii (PCP). **Malignosti** Zelo redko so poročali tudi o primerih mielodisplastičnega sindroma in sekundarnih malignostih, vključno z mieloidno levkemijo. Antiemetično zdravljenje Navzea in bruhanje sta pogosto povezana z zdravljenjem s TMZ. **Antiemetično zdravljenje** se lahko da pred uporabo TMZ ali po njej. **Odrasli bolniki z novo diagnosticiranim multiformnim glioblastomom** Antiemetična profilaksa je priporočljiva pred začetnim odmerkom sočasne faze in je močno priporočljiva med fazo monoterapije. **Ponavljajoči se ali napredujoči maligni gliom** Pri bolnikih, ki so močno bruhali (stopnja 3 ali 4) v prejšnjih ciklih zdravljenja, je potrebno antiemetično zdravljenje. **Laboratorijske vrednosti** Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC ≥ 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 > 1,5 x 109/l in število trombocitov > 100 x 109/l. Če med katerimkoli ciklom ANC pade na < 1,0 x 109/l ali število trombocitov na < 50 x 109/l, morate odmerek zdravila v naslednjem ciklu zmanjšati za eno stopnjo (glejte poglavje 4.2). Stopnje odmerka so 100 mg/m2, 150 mg/m2 in 200 mg/m2. Najmanjši priporočeni odmerek je 100 mg/m2. **Pediatrična uporaba** Kliničnih izkušenj z uporabo TMZ pri otrocih, mlajših od 3 let, ni. Izkušnje z uporabo tega zdravila pri starejših otrocih in mladostnikih so zelo omejene. **Starejši bolniki (stari > 70 let)** Videti je, da je pri starejših bolnikih tveganje za nevtropenijo ali trombocitopenijo večje, kot pri mlajših. Zato je pri uporabi zdravila TMZ pri starejših bolnikih potrebna posebna previdnost. **Moški bolniki** Moškim, ki se zdravijo s TMZ je treba svetovati, naj ne zaplodijo otroka še šest mesecev po prejetem zadnjem odmerku in naj se pred zdravljenjem posvetujejo o možnostih za shranitev zmrznjene sperme. **Natrij** To zdravilo vsebuje 2,4 mmol natrija na vialo. To je treba upoštevati pri bolnikih na nadzorovani dieti z malo natrija. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študije medsebojnega delovanja so izvedli le pri odraslih. V ločeni študiji 1. faze, sočasna uporaba TMZ in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali izpostavljenosti njegovem aktivnem presnovku monometiltriazenoimidazol karboksamidu (MTIK). Analiza populacijske farmakokinetike v preskušanjih 2. faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka TMZ. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično pomembnim zmanjšanjem očistka TMZ. Študij za določitev učinka TMZ na presnovo ali izločanje drugih zdravil niso izvedli. Ker pa se TMZ ne presnavlja v jetrih in se na beljakovine veže le v majhni meri, je malo verjetno, da bi vplival na farmakokinetiko drugih zdravil. Uporaba TMZ v kombinaciji z drugimi mielosupresivnimi učinkovinami lahko poveča verjetnost mielosupresije. **Neželeni učinki:** Pri bolnikih, ki se zdravijo s TMZ v kombinaciji z RT ali monoterapijo po RT zaradi novo diagnosticiranega multiformnega glioblastoma ali z monoterapijo pri bolnikih s ponavljajočim se ali napredujočim gliomom, so bili zelo pogosti neželeni učinki podobni; slabost, bruhanje, zaprtje, neješčnost, glavobol in utrujenost. Pri bolnikih z novo diagnosticiranim glioblastomom multiforme na monoterapiji so zelo pogosto poročali o konvulzijah, medtem ko je bil izpuščaj opisan zelo pogosto pri bolnikih z novo diagnosticiranim multiformnim glioblastomom, ki so prejemali TMZ sočasno z RT, ter pri tistih, ki so zdravilo prejemali v obliki monoterapije, pogosto pa pri tistih s ponavljajočim se gliomom. Pri obeh indikacijah so o večini hematoloških neželenih reakcij poročali pogosto ali zelo pogosto. **Imetnik dovoljenja za promet:** Schering-Plough Europe, Rue de Stalle 73, Bruselj Belgija **Način in režim izdaje zdravila: Zdravilo Temodal 20 mg, 100 mg, 140mg, 180 mg, 250 mg** se izdaja na recept (Rp/Spec), Temodal 2,5 mg/ml prašek za raztopino za infundiranje pa je namenjeno uporabi samo v bolnišnicah (H). **Datum priprave informacije:** februar 2010

Literatura: 1 Povzetek temeljnih značilnosti zdravila Temodal 2 Stupp R, et. al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised III study: 5-year analysis of the EORTC-NCIC trial

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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 samostojno vzdrževalno zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč s stabilno boleznijo po 4 ciklih standardne kemoterapije na osnovi platine v prvi liniji zdravljenja. Zdravilo Tarceva je indicirano tudi 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 je treba zmanjševati 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: 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 treba zdravljenje z zdravilom Tarceva prekiniti, dokler ni znana diagnoza. Bolnike, ki se sočasno zdravijo z erlotinibom in gemcitabinom, je treba skrbno spremljati zaradi možnosti pojava toksičnosti, podobni intersticijski bolezni pljuč. Če je ugotovljena intersticijska bolezen pljuč, zdravilo Tarceva ukinemo in uvedemo ustrezno zdravljenje. Pri približno polovici bolnikov, ki so se zdravili z zdravilom Tarceva, se je pojavila driska (vključno z zelo redkimi primeri, ki so se končali s smrtnim izidom). 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 treba zdravljenje z zdravilom Tarceva 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 (vključno z nekaterimi primeri, ki so se končali s smrtnim izidom). 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 divertikularno bolezen, 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 učinkov, 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 *kumarinske antikoagulante*, je treba redno kontrolirati protrombinski čas ali INR. Sočasno zdravljenje z zdravilom Tarceva in *statinom* lahko poveča tveganje za miopatijo, povzročeno s statini, vključno z rabdomiolizo; to so opazili redko. 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, navzea, bruhanje, stomatitis, bolečina v trebuhu, pruritus, suha koža, suhi keratokonjunktivitis, konjunktivitis, zmanjšanje telesne mase, depresija, glavobol, nevropatija, dispepsija, flatulenca, alopecija, okorelost, pireksija, nenormalnosti testov jetrne funkcije. *Pogosti neželeni učinki* so krvavitve v prebavilih, epistaksa, keratitis, paronihija, fisure na koži. *Občasno* so poročali o perforacijah v prebavilih, hirzutizmu, spremembah obrvi, krhkih nohtih, odstopanju nohtov od kože, blagih reakcijah na koži (npr. hiperpigmentacija), spremembah trepalnic, hudi intersticijski bolezni pljuč (vključno s smrtnimi primeri). *Redko* pa so poročali o jetrni odpovedi. *Zelo redko* so poročali o Stevens-Johnsonovem sindromu/toksični epidermalni nekrolizi 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:** 2.0/10. **Informacija pripravljena:** november 2010.

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ČAS ZA ŽIVLJENJE.

DOKAZANO PODALJŠA PREŽIVETJE PRI BOLNIKIH:

- z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč[1]
- z metastatskim rakom trebušne slinavke[1]

[1] Povzetek glavnih značilnosti zdravila TARCEVA, www.ema.europa.eu

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA Epufen 12,5, 25, 50, 100 in 150 mikrogramov/uro transdermalni obliži SESTAVA: 1 transdermalni obliž vsebuje 2,89 mg, 5,78 mg 11,56 mg, 23,12 mg ali 34,65 mg fentanila. **TERAPEVTSKE INDIKACIJE:** Huda kronična bolečina, ki se lahko ustrezno zdravi le z opioidnimi analgetiki. **ODMERJANJE IN NAČIN UPORABE:** Odmerjanje je treba individualno prilagoditi ter ga po vsaki uporabi redno oceniti. Izbira začetnega odmerka: velikost odmerka fentanila je odvisna od predhodne uporabe opioidov, kjer se upošteva možnost pojava tolerance, sočasnega zdravljenja, bolnikovega splošnega zdravstvenega stanja in stopnje resnosti obolenja. Pri bolnikih, ki pred tem niso dobivali močnih opioidov, začetni odmerek ne sme preseči 12,5-25 mikrogramov na uro. Zamenjava opioidnega zdravljenja: pri zamenjavi peroralnih ali parenteralnih opioidov s fentanilom je treba začetni odmerek izračunati na osnovi količine analgetika, ki je bila potrebna v zadnjih 24 urah, jo pretvoriti v odgovarjajoči odmerek morfina s pomočjo razpredelnice in nato preračunati ustrezen odmerek fentanila, spet s pomočjo razpredelnice (glejte SmPC). Prvih 12 ur po prehodu na transdermalni obliž Epufen bolnik še vedno dobiva predhodni analgetik v enakem odmerku kot prej; v naslednjih 12 urah se ta analgetik daje po potrebi. Titracija odmerka in vzdrževalno zdravljenje: obliž je treba zamenjati vsakih 72 ur. Odmerek je treba titrirati individualno, dokler ni dosežen analgetični učinek. Odmerek 12,5 mikrogramov/uro je primeren za titriranje odmerka v manjšem odmernem območju. Če analgezija na koncu začetnega obdobja nošenja obliža ni zadostna, se lahko odmerek po 3 dneh zveča. Možno je, da bodo bolniki potrebovali občasne dodatne odmerke kratko delujočih analgetikov (npr. morfina) za prekinitev bolečine. Sprememba ali prekinitev zdravljenja: vsaka zamenjava z drugim opioidom mora potekati postopoma, z majhnim začetnim odmerkom in počasnim zvečevanjem. Splošno veljavno pravilo je postopna ustavitev opioidne analgezije, da bi preprečili odtegnitvene simptome, kot so navzeja, bruhanje, diareja, anksioznost in mišični tremor. Uporaba pri starejših bolnikih: starejše in oslabljene bolnike je treba skrbno opazovati zaradi simptomov prevelikega odmerjanja ter odmerek po potrebi zmanjšati. Uporaba pri otrocih: transdermalni obliži Epufen se lahko uporabljajo le pri pediatričnih bolnikih (starih od 2 do 16 let), ki tolerirajo opioide in peroralno že dobivajo opioide v odmerku, enakovrednemu najmanj 30 mg morfina na dan. Bolnik mora prvih 12 ur po prehodu na Epufen še vedno dobivati predhodni analgetik v enakem odmerku kot prej. V naslednjih 12 urah je treba ta analgetik dajati odvisno od kliničnih potreb. Titracija odmerka in vzdrževalno zdravljenje: če je analgetični učinek Epufena prešibak, je treba bolniku dodati morfin ali drugi opioid s kratkim delovanjem. Odvisno od dodatnih potreb po analgeziji in jakosti bolečine pri otroku se lahko uporabi več obližev. Odmerek je treba prilagajati korakoma, po 12,5 mikrogramov/uro. Uporaba pri bolnikih z jetrno ali ledvično okvaro: Zaradi možnosti pojava simptomov prevelikega odmerjanja je treba te bolnike skrbno spremljati in odmerek ustrezno zmanjšati. Uporaba pri bolnikih s povečano telesno temperaturo: Pri teh bolnikih bo morda treba prilagoditi odmerek. **Način uporabe:** transdermalni obliž Epufen je treba takoj po odprtju vrečke nalepiti na nerazdraženo, neobsevano kožo, na ravno površino prsnega koša, zgornjega dela hrbta ali nadlakti. Po odstranitvi zaščitne plasti je treba obliž trdno pritrditi na izbrano mesto in z dlanjo pritiskati približno 30 sekund, da se obliž popolnoma nalepi, še zlasti na robovih. Uporaba pri otrocih: pri mlajših otrocih je obliž priporočljivo nalepiti na zgornji del hrbta, ker je manjša verjetnost, da bi otrok odstranil obliž. Transdermalnega obliža se ne sme deliti, ker podatkov o tem ni na voljo. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino, hidrogenirano kolofonijo, sojo, arašide ali katerokoli pomožno snov. Akutna ali pooperativna bolečina, ko v kratkem časovnem obdobju ni možno titriranje odmerka in obstaja verjetnost za življenjsko ogrožajočo respiratorno depresijo. Huda okvara osrednjega živčnega sistema. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Zaradi razpolovne dobe fentanila je treba bolnika v primeru pojava neželenega učinka opazovati še 24 ur po odstranitvi obliža. Pri nekaterih bolnikih, ki uporabljajo transdermalni obliž Epufen, se lahko pojavi respiratorna depresija. Epufen je treba previdno dajati: bolnikom s kronično pljučno boleznijo, zvišanim intrakranialnim tlakom, možganskim tumorjem, boleznimi srca, jeter in ledvic, tistim z zvišano telesno temperaturo, pri starejših bolnikih in otrocih, bolnikih z miastenijo gravis. Odvisnost od zdravila: kot posledica ponavljajoče se uporabe se lahko razvijeta toleranca na učinkovino ter psihična in/ali fizična odvisnost od nje. Ostali: lahko se pojavijo neepileptične (mio)klonične reakcije. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Derivati barbiturne kisline, opioidi, anksiolitiki in pomirjevala, hipnotiki, splošni anestetiki, fenotiazini, mišični relaksanti, sedativni antihistaminiki in alkoholne pijače, zaviralci MAO, itrakonazol, ritonavir, ketokonazol, nekateri makrolidni antibiotiki, pentazocin, buprenorfin. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo ima močan vpliv na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI:** Najbolj resen neželen učinek fentanila je respiratorna depresija. Zelo pogosti (≥ 1/10): dremavost, glavobol, navzeja, bruhanje, zaprtje, znojenje, srbenje, somnolenca. Pogosti (≥ 1/100 do < 1/10): kserostomija, dispepsija, reakcije na koži na mestu aplikacije, sedacija, zmedenost, depresija, tesnoba, živčna napetost, halucinacije, zmanjšan apetit. 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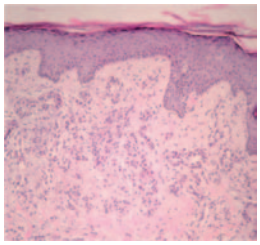

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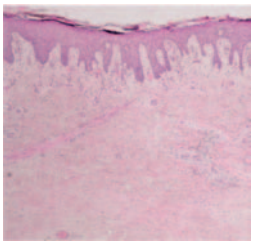

Quaglino P, Annals Of Surgical Oncology. 15 (8):2215-2222. 2008

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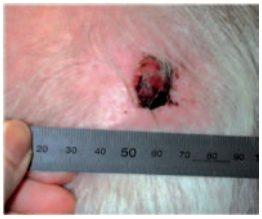

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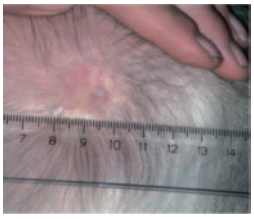

Gehl J, EJC Supplements, Volume 4, N° 11:35-37, 2006

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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.

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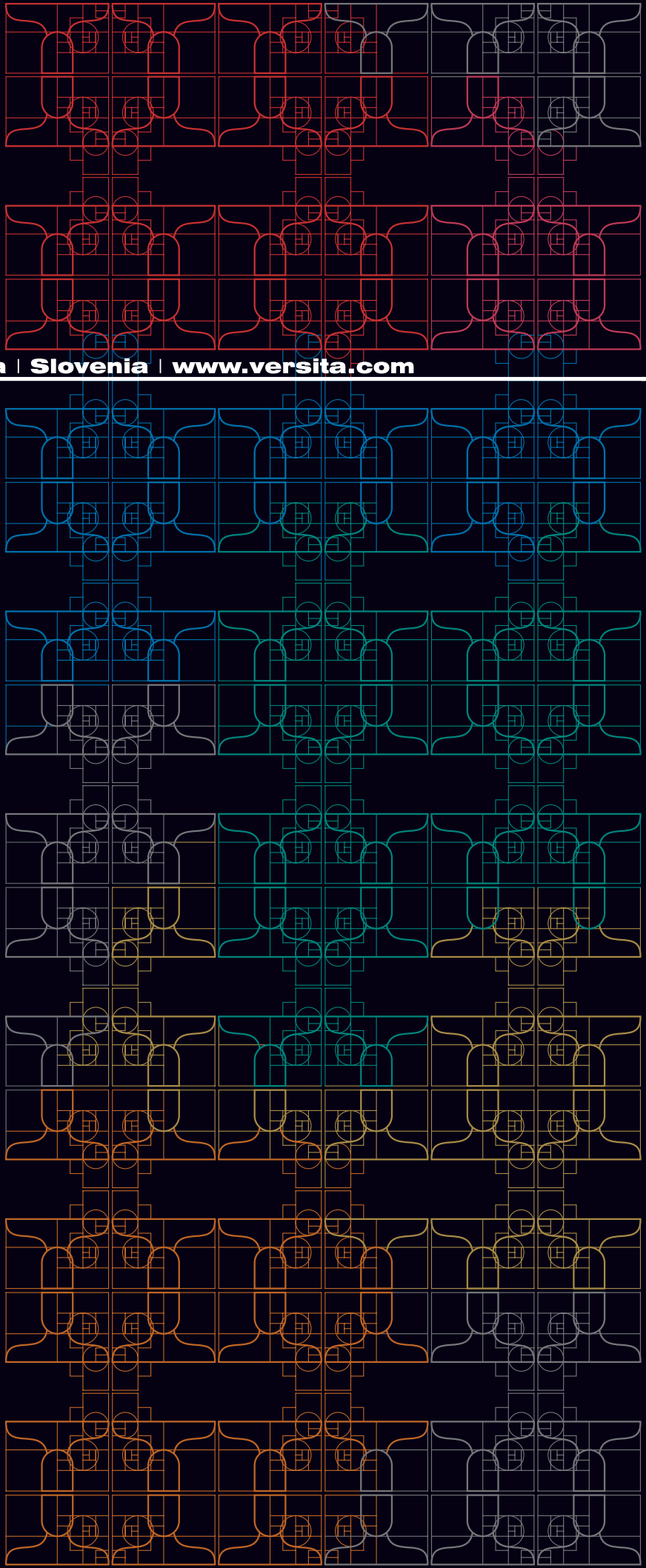

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