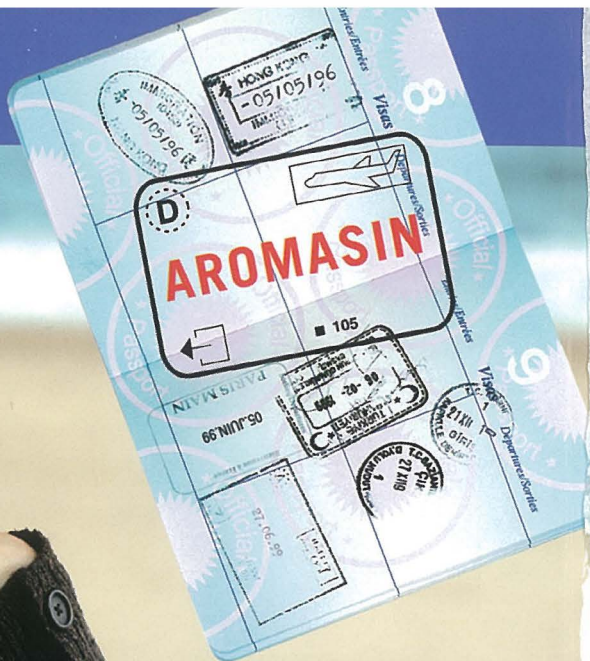


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review

Imaging of small amounts of pleural fluid. Part two - physiologic pleural fluid

Igor Kocijančič

Department of Radiology, Institute of Oncology, Ljubljana, Slovenia

Background. There are only a few articles reporting the possibility of radiographic and sonographic detection of physiologic pleural fluid in healthy individuals. In the last decade the advent of sonographic equipments enables the detection of small amounts of physiologic pleural fluid in about 20% of healthy individuals. In certain physiologic conditions (i.e. pregnancy) the physiologic pleural fluid could be detected more frequently by chest ultrasonography.

Conclusions. A positive result, if detected, should not be taken as a sign of the occult thoracic disease.

Key words: pleura; pleural effusion; radiography, thoracic

Introduction

The pleural space is the extremely thin, well-defined liquid space which facilitates the sliding of lung within the chest cavity. A small amount of fluid in the pleural space acts as an efficient lubricating layer which minimizes energy losses during the respiration and maximizes the transmission of forces from the chest wall to the lung.¹

Limited studies in healthy human volunteers indicate that the volume of fluid is generally no more than 5 ml, but may be as much as 15 to 20 ml.² In a recent report Noppen *et al.*³ showed that the amount of pleural fluid in

a single pleural space is 4 to 13 ml. They accessed the pleural cavity in 34 otherwise healthy subjects treated with thoracoscopic sympatcolysis for the severe essential hyperhidrosis.

In the literature there are only few articles reporting the possibility of imaging of physiologic pleural fluid. There are only two articles,^{4,5} both over 50 years old, reporting on the use of lateral decubitus radiography for demonstrating normal pleural fluid in healthy individuals. With the advent of sonography it was shown that very small amounts of pleural fluid can be demonstrated this way.

If the amount of pleural fluid is small, it is mostly adherent to the pleural surface and for that reason it is essentially invisible by imaging methods. When the amount of pleural fluid approaches towards 15 ml, it becomes free within the pleural cavity, particularly at costophrenic recesses, around the hilar and lobar margins⁶ and it then becomes potential-

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ly visible by imaging methods. There is no clear border between the amount of pleural fluid in physiologic and pathologic (i.e. effusion as a sign of pleural disease) conditions.

Lateral decubitus chest radiography

Lateral decubitus chest radiographs were used for many years for the diagnosis of small pleural effusions, but there are only two articles,^{4,5} both over 50 years old, reporting on the use of lateral decubitus radiography for demonstrating normal pleural fluid in healthy individuals. Hessen⁴ improved the technique with the central beam aimed at the lateral chest wall, together with the elevation of the patient's hip. He found physiologic pleural fluid layer of 3 mm or more in 12 cases of 300 healthy volunteers. The exposure in expiration is mentioned in the work of Müller and Löfstedt,⁵ but apparently without gaining wider acceptance. They examined 120 healthy persons by their method and observed fluid in 11 cases. They also performed thoracentesis and found that the amount of fluid was 3- 15 ml.

Both techniques (patient's position during examination and exposure in suspended expiration) were applied in the study of Kocijančič *et al.*^{7,8} in 106 healthy volunteers, but they

found only one case of pleural fluid layer in the lateral decubitus position (Figure 1). So our conclusion is that *physiologic pleural fluid visible on lateral chest radiography is an extremely rare condition*. In every such case the pleural disease or pleural involvement should be considered.

Hessen⁴ also examined 92 women 6 to 10 days after delivery with lateral chest radiography and found pleural fluid layer in 21 cases. This "physiologic" condition is nowadays well known as "benign postpartum pleural effusion".^{9,10}

Chest ultrasonography

In the last decades ultrasonography (US) of pleural space becomes a leading real-time method for demonstrating small pleural effusions.¹¹⁻¹⁵

Kocijančič *et al.*⁷ in a preliminary study of 106 healthy volunteers showed that physiologic pleural fluid layer of 2 mm or more could be detected in experimental conditions in 25% of persons. They performed chest US of the lower pleural space throughout a 15 by 20 cm opening in the special examination table after 5 minutes leaning in the lateral decubitus position, the same position as in lateral decubitus chest radiography. In decubi-

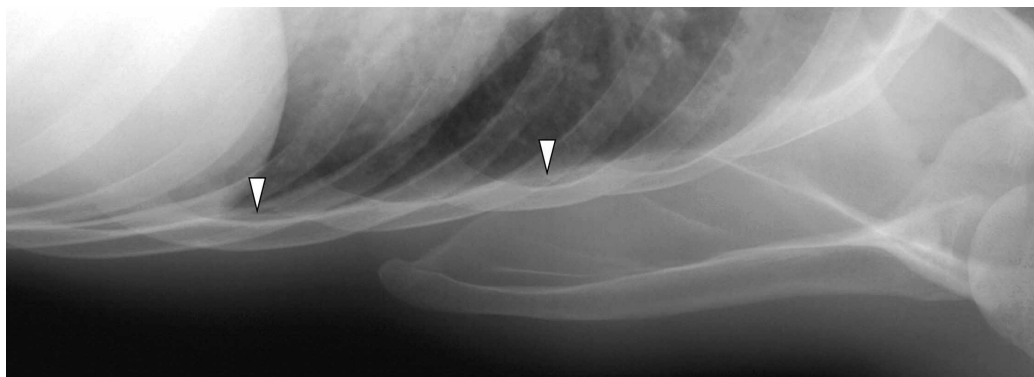


Figure 1. Left lateral decubitus expiratory radiograph showing 3 mm thick density with horizontal level (arrowhead over phrenicocostal sinus), consisting with criterion defining pleural fluid. Medial margin of the scapula should not be misinterpreted as pleural fluid accumulation (arrowhead at the level of 4th rib).

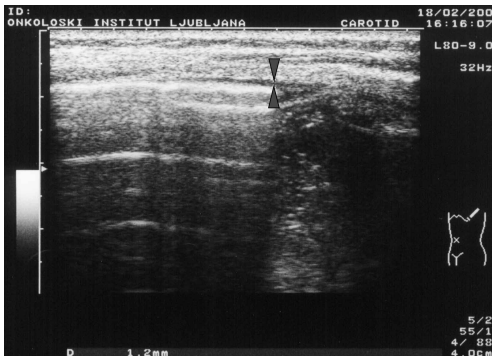


Figure 2a. Sonographic examination of the left pleural space in decubitus position. After 2 minutes laying less than 2 mm thick anechoic fluid layer (between arrowheads) appeared.

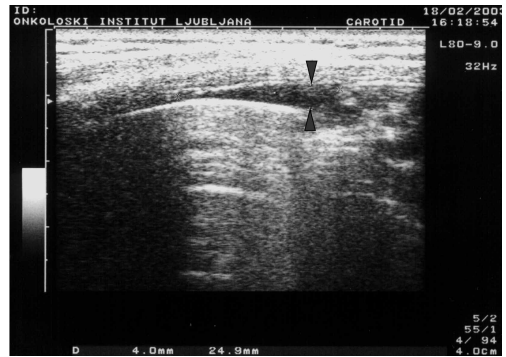


Figure 2b. Sonographic examination of the left pleural space in decubitus position. Three minutes later typically wedge-shaped 4 mm thick fluid layer was observed (between arrowheads)

tus position the pleural space was interrogated several times searching for the fluid accumulation (Figure 2). They repeated the examination of lower pleural space with the subject leaning on the elbow, still in the lateral decubitus position. In this so called "elbow position" (Figure 3) there were no instances in which fluid was only detected whilst in the lateral decubitus position.

In the follow up study they repeated chest US on each subject after two to four months.¹⁶ They suggest that there are individuals with US permanently less ("dry pleural space") or more ("wet pleural space") physiological pleural fluid (Figure 4).

In these reports they determined US criteria for physiologic pleural fluid: *at least 2 mm thick (but not exceeding 5 mm) anechogenic zone between the parietal and the visceral pleura and/or changing of fluid layer thickness between expiration and inspiration as well as changing with different positions of the patient.*^{7,16}

In the majority of cases (75%), physiologic pleural fluid has wedge-shaped appearance on chest US (Figures 3, 4), while in the remaining cases anechoic fluid was visible between two parallel pleural lines. As the US examination is a real time method it is very important that all sonographic measurements with the probe perpendicular to the thoracic wall should be done.

Results of a pilot study of pleural space US in 47 healthy pregnant by Kocijančič *et al.*¹⁷ confirmed physiologic pleural fluid in 60% of perfectly health pregnant. Such a positive result, if isolated, should not be taken as a sign of occult thoracic disease (Figure 5).

Conclusions

The physiologic pleural fluid could evidently be an important source of error in the diagnosis of pleural effusion by imaging methods, at first by chest US.

In the cases of the so called "wet pleural space" chest US showed the fluid layer more accurately than radiography does. The possi-

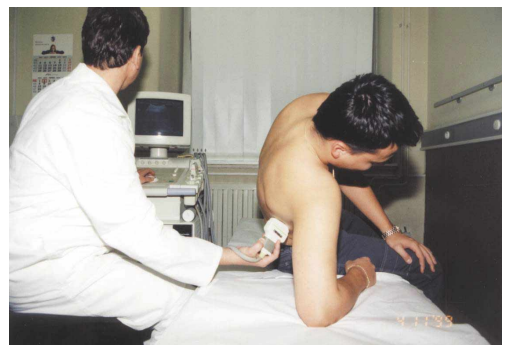


Figure 3. A photograph showing the position of the patient, the probe and the examiner during the examination of the right pleural space.



Figure 4a. US examination of the right pleural space in the elbow position. A baseline study showed typically wedge-shaped 3 mm thick fluid layer (between calipers).

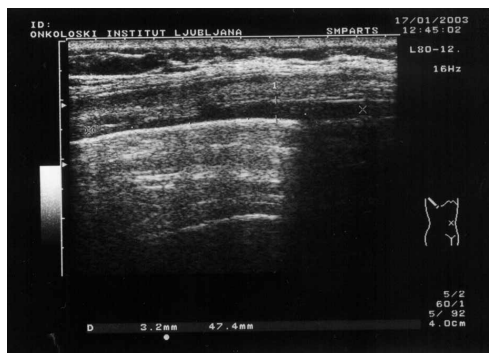


Figure 4b. US examination of the right pleural space in the elbow position. In the follow up study three months later the fluid layer (between calipers) of almost the same thickness was found.

ble reasons are: flexibility of US perpendicular approach compared to chest radiography in which the beam is tangential, clear US contrast of pleural fluid compared to adjacent structures (radiographically the density of the fluid and the bone are very near) and technically improved ultrasound scanners.

Chest US should be introduced for patients with diseases frequently affecting pleura, such as systemic connective tissue diseases and certain neoplasms. The aim of such examination would be to establish the baseline status of pleural space (e.g. if visible pleural fluid is present before the treatment). The subsequent examination in the case of disease progression would thus enable us to

identify small pleural effusion as an early sign of pleural involvement.

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Figure 5a. US of the right lower pleural space in a sitting position. Approximately 5 mm thick pleural fluid layer (between arrows); L=liver.

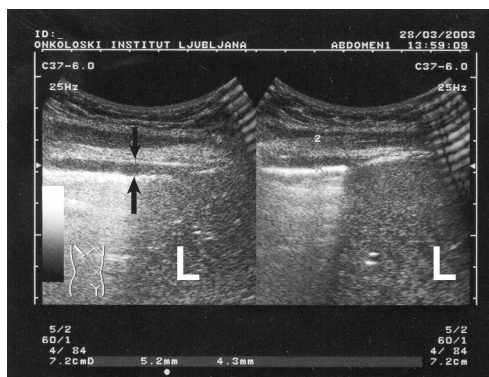


Figure 5b. US of the right lower pleural space in a sitting position. Detection of fluid using abdominal large radius convex probe (between arrows); L=liver.

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The estimation of the value and mobility of Parks' angle in case-series of patients with defecatory disorders - prospective clinical examination supplemented with the defecographic examination

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Background. Defecography is used by a majority of colorectal surgeons for it is the only method for anatomic and dynamic studies of the act of defecation. The method provides information on different aspects of anorectal and pelvic floor function and offers the possibility of visualizing the development of anatomic abnormalities.

Methods. We analyzed the defecography findings carried out at 56 patients (50 female and 6 male) from 24 to 83 years of age (the average age 58.3 years) with proctologic ailments such as: faecal incontinence, sensation of obstruction in the rectum, constipations, rectal prolapse, solitary ulceration of rectum. The values of Parks' angle (ARA - the anorectal angle) were measured at rest, at strain and during defecation. Other parameters measured included: duration of sphincter relaxation, overall duration of defecation, mobility of the pelvic diaphragm.

Results. Abnormal values of Parks' angle at rest and at strain were found in patients with the following problems: faecal incontinence, sensation of obstruction in rectum and constipation. However, they did not turn out to be characteristic for patients with rectal prolapse. Defecography has helped to detect concomitant rectoceles in patients suffering from constipation and sensation of obstruction in the rectum. Defecography has also proved to be effective in the evaluation of patients who suffered from solitary ulceration of rectum. During the examination of these patients it has been observed that Parks' angle in various phases of defecation has flattened. The duration of sphincter relaxation in the studied group was changeable and did not depend on the kind of pathology.

Conclusions. Defecography is one of the examinations which can be helpful in the evaluation of patient's motor functions both before and after the operation.

Key words: constipation; faecal incontinence; defecography

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Introduction

The complex mechanism of defecation is controlled by both the central nervous system and the medullar centres. One of the steps of defecation reflex is the relaxation of sphincter muscles (puborectal and external anal sphincter) and the widening of the anorectal angle (ARA) of Parks', caused by the activated sensation of tenesmus of the central nervous system.

There are several factors which affect the defecation activity: volume and consistency of faeces, capacity of the rectal ampulla and susceptibility of the rectum wall, continence of sphincter muscles, sensory mechanism, mechanical factors such as: pelvis floor muscles, and value of the ARA of Parks'. Recognized as the necessary condition for normal human continence, Parks' angle is formed between the longitudinal axis of the rectum and the axis of the anal canal and created by applying traction on the rectum by stretched puborectal muscle.¹

Today, defecography is used by a majority of colorectal surgeons for it is the only method for anatomic and dynamic studies of the act of defecation.² The method provides information on different aspects of anorectal and pelvic floor function and offers the possibility of visualizing the development of anatomic abnormalities.²

Although the number of investigations has questioned the significance of the ARA in the maintenance of faecal incontinence, the configurational changes of the ARA with voluntary contraction or relaxation of the pelvic floor may be important.³ Furthermore, many clinicians continue to place credence in the ARA, and routine measurements are often taken.³ In this paper we present the application of defecography in the measurement of the ARA and the findings in defecography in patients with disturbed defecation.

Methods

A group of 56 consecutive patients (50 females and 6 males) from 24 to 83 years of age (the average age 58.3 years old) who suffered from defecation activity disorders in the form of:

- constipation,
 - sensation of obstruction or incomplete defecation,
 - faecal incontinence,
 - rectal prolapse,
 - solitary ulcer of rectum
- were examined.

Each patient was qualified for defecography by the surgeon. Prior to the examination the medical history of these patients was taken including information about past diseases, injuries and child-birth, in the case of the female patients. The patients' continence for gas and faeces was evaluated with the Wexner scale. They also underwent the usual proctologic investigation and rectoscopy. Finally, the defecographic examination was performed by an experienced radiologist. Whole diagnostics were performed by one team of doctors.

Informed consent was obtained after the nature of the procedures had been fully explained to the patients, and the study was approved by the Medical Academy authorities.

The technique of defecographic examination

The patients were prepared in a similar way as for the enema examination. The day before the investigation they took X-Prep or Fortrans. The contrast medium used for the examination was barium sulphate suspension concentrated with starch (solution of boiled potato flour) in order to obtain the thick consistency similar to the consistency of stool. The contrast medium was administered per rectum through Foley's catheter in the amount enough to fill the splenic flexure of the colon. The examination was carried out in

two stages. During the first stage, after the application of the contrast medium in the recumbent position, the patient was seated on a plastic bucket and then the catheter was withdrawn. The patient was asked to bear down as if to defecate.

The examination was recorded on a magnetic tape and the durations of the sphincter relaxation and the overall defecation were measured. The duration of sphincter relaxation is the time measured between the beginning and the end of widening of the anal canal. The overall duration of defecation is the time needed for passing stools.⁴ The recording was made in video technique with PANASONIC UCR/TV camera and XD PRO SUPER UMS 180 tape. During the second stage three x-ray films were taken: at rest, during the defecation and in the phase of maximum contraction. The x-ray films taken in 35 x 35 mm format were later used for measuring precisely the anorectal angle and evaluating the pelvis floor mobility. The films also allowed for the evaluation of the size of rectocele.

During defecography the following parameters were estimated: ARA and its dynamics,^{3,5} duration of sphincter relaxation and

overall duration of defecation. ARA was formed at intersection of the line running along the axis of the anal canal and the tangent line to the posterior wall of the rectum. The proper value of this triangle at rest is 95 - 105°. During the defecation the angle should increase (up to about 150°) and during the contraction it should decrease up to about 80°. The mobility of pelvic diaphragm was estimated on the basis of lowering of the anorectal junction in relation to the ischiadic tubers. The accepted standard was the lowering of anorectal junction not exceeding 3.5 cm during tenesmus.⁶ In addition, the distance of the rectal posterior wall from the sacral bone was measured. The recording of the defecographic examination on the video tape allowed estimating individual stages of the defecation.

Results

Tables 1-6 show the results for six separate groups of patients depending on the ailment and the course of the disease.

Thirteen patients with symptoms of gas and faecal incontinence were examined

Table 1. Patients with faecal incontinence

No.	Age	Sex	No of births	Parks' angle at rest	Parks' angle at contraction	Parks' angle at defecation	Rectocele	Wexner scale	Pelvic floor mobility (cm)	Total defecation time/s/
1	77	M	-	110	90	115	-	3	<1	10
2	66	F	2	110	110	145	-	12	>1	10
3	51	F	2	150	100	120	Big	14	<5	8
4	73	F	2	115	110	120	-	14	<5	20
5	49	M	-	100	95	125	-	3	<5	17
6	69	F	4	85	80	90	-	4	<3	7
7	55	F	1	115	105	125	-	17	<7	10
8	35	F	1	120	110	118	-	14	<1	35
9	56	F	1	110	110	120	-	8	<1	10
10	73	F	-	117	108	123	Big	4	<5	30
11	57	F	-	118	112	125	Small	10	1	32
12	72	F	2	120	120	135	-	17	4	5
13	51	F	1	115	98	132	Big	12	4	17

Table 2. The patients who felt sensation of obstruction or incomplete defecation

No.	Age	Sex	No of births	Parks' angle at rest	Parks' angle at contraction	Parks' angle at defecation	Rectocele	Wexner scale	Pelvic floor mobility (cm)	Total defecation time/s/
1	55	F	2	110	80	120	little	0	≤1cm	20
2	59	F	3	115	95	125	-	0	≤2cm	110
3	55	F	1	95	95	105	little	0	≤10cm	10
4	46	F	-	120	110	112	-	1	≤1,5cm	125
5	45	F	2	115	110	135	big	0	≤2cm	12
6	30	M		95	85	115	-	3	≤4cm	150
7	59	F	4	105	95	125	little	2	≤5cm	240
8	63	F	-	105	95	110	-	1	≤5cm	45
9	73	F	2	95	86	115	big	2	≤4cm	25
10	69	F	1	133	120	130	little	0	≤3cm	32
11	65	F	2	90	80	180		14	≤1cm	3
12	35	M		115	105	122		0	≤3,5cm	41
13	60	F	1	95	90	115	little	8	≤4cm	6

(Table 1). In 1 case a small rectocele was detected which had not been discovered initially by means of the proctologic examination. In 3 other cases a big rectocele was detected. Other 11 patients were characterized by too obtuse Park's angle at rest and did not decrease during contractions. Two patients had the right angle. In 9 out of 13 cases Parks' angle did not decrease during the contraction. The lowering of pelvis floor mobility was detected in 7 cases. The overall duration of defecation did not turn out to be characteristic. The value of ARA in these cases was mostly incorrect.

Thirteen patients, who felt sensation of obstruction or incomplete defecation, were examined (Table 2). In 8 cases ARA at rest was abnormally obtuse but in 9 cases it was properly acute during contractions. Rectocele, not diagnosed initially during palpation, was detected at 6 patients; in 2 of them it was big.

The overall duration of defecation lengthened; in 1 case it amounted to 2.5 minutes. Most of the patients in this group had abnormally obtuse Parks' angle at rest and the overall duration of defecation was lengthened.

Another group consisted of 2 female patients with solitary ulcer of rectum (Table 3). These patients were characterized by "flattening" of the value of Parks' angle during various stages of defecation. In both cases ARA did not decrease during the contraction and the overall duration of defecation lengthened. The pelvis floor mobility was in both cases normal. Defecography turned out to be useful at examining patients with this rare disease. Values of Parks' angle in various stages of the defecographic examination got flattened (the lack of dynamics of ARA during defecation) and the overall duration of defecation lengthened.

There were 10 patients with rectal pro-

Table 3. Patients with solitary rectal ulcer

No.	Age	Sex	No of births	Parks' angle at rest	Parks' angle at contraction	Parks' angle at defecation	Rectocele	Wexner scale	Pelvic floor mobility (cm)	Total defecation time/s/
1	37	F	-	108	110	118	-	0	1,5cm	40
2	66	F	1	155	125	155	-	0	1,5cm	14

Table 4. Patients with rectal prolapse

No.	Age	Sex	No of births	Parks' angle at rest	Parks' angle at contraction	Parks' angle at defecation	Rectocele	Wexner scale	Pelvic floor mobility (cm)	Total defecation time/s/
1	81	F	4	*	*	*	-	13	*	*
2	80	F	-	*	*	*	-	14	*	*
3	47	F	4	*	*	*	-	16	*	*
4	24	M	-	95	80	115	-	0	4	7
5	72	F	3	95	120	140	Big 7-8 cm	2	7	10
6	50	M	-	110	80	180	-	0	1	20
7	70	F	2	128	127	140	4cm	0	4	25
8	61	F	1	??	??	?	-	8	4	15
9	74	F	1	120	107	140	-	16	*	*
10	65	F	1	85	87	140	-	16	*	47

*Due to technical difficulties not all the parameters have been measured.

lapse (Table 4). Three of them could not undergo the examination due to technical reasons, i.e. the complete incontinence of contrast medium. In 2 cases the examination helped to detect rectocele (1 was big). The overall duration of defecation was lengthened in 4 cases. The pelvic floor was abnormally lowered in 2 cases. In 3 cases abnormally obtuse ARA was detected. Values of ARA did not turn out to be characteristic for the group of patients with rectal prolapse.

The group, who is characterized by symptoms of constipation, consisted of 12 patients

(Table 5). The overall duration of defecation was lengthened in 4 cases and in the remaining 8 cases it was within the normal range. Rectocele was found in 9 patients: a small one in 2 cases, a medium one in 6 cases, and a big one in 1 case. In 5 cases ARA during contraction did not decrease which was abnormal. In six cases abnormally obtuse ARA was detected at rest.

The last group consists of 2 female patients who could not be assigned to any other group of proctologic ailments (Table 6). One of them had undergone rectopexy and the

Table 5. The patients with obstruction

No.	Age	Sex	No of births	Parks' angle at rest	Parks' angle at contraction	Parks' angle at defecation	Rectocele	Wexner scale	Pelvic floor mobility (cm)	Total defecation time/s/
1	79	F	2	135	95	135	-	0	≤4	10
2	69	F	3	120	90	135	-	0	≤2	15
3	77	F	-	143	135	155	-	0	≤12	8
4	55	F	-	103	95	118	little	6	≤2	22
5	66	F	1	123	129	148	middle	0	≤6,8	19
6	53	F	1	105	80	100	middle	0	≤3	10
7	47	F	-	70	80	100	middle	0	≤2,4	20
8	31	F	-	97	84	132	big	0	≤2	10
9	44	F	2	115	115	120	middle	2	≤4	10
10	26	F	-	127	120	143	middle	0	≤2	18
11	57	F	-	72	66	70	middle	0	≤5	15
12	72	F	-	105	105	150	little	0	≤3	15

Table 6. Others disorders

No.	Age	Sex	No of births	Kind of disorder	Parks' angle at rest	Parks' angle at contraction	Parks' angle at defecation	Rectocele	Wexner scale	Pelvic floor mobility (cm)	Total defecation time
1	48	F	1	Following rectopexy	100	100	135		5	4	10
2	48	F	2	Following surgery on recto-vaginal fistula	95	92	100		0	5	30

other post partum plastic operation of recto-vaginal fistula protected with transversostomy. The former was characterized by low dynamics of ARA during defecation and the lack of decreasing the angle during contractions. Unfortunately no examination was carried out due to the complete incontinence of contrast medium caused by the full wall rectal prolapse. The examination could not be comparative in relation to the pre-operative condition of the patient.

In the case of the patient with post partum plastic operation of rectovaginal fistula protected with transversostomy the fistula was not detected. ARA during defecation got flattened; there were very small differences between the various stages of defecation. The overall duration of defecation lengthened more than twice. These disorders might have been caused with the temporary exclusion of the last segment of alimentary tract.

Additionally to the above presented groups of patients, four underwent the examination simultaneously in two groups. There were two patients with symptoms of rectal prolapse and faecal incontinence and another two patients with constipation and sensation of the obstruction. In each group the duration of sphincter relaxation was individually variable and did not depend on the pathology.

Discussion

Defecation activity disorders may occur on a different level and their causes are not always easy to diagnose. In order to evaluate the

causes affecting the defecation a number of methods is used, such as: anorectal manometry, transrectal ultrasound, electromyography, magnetic resonance and others. The significance of defecography and especially its value in measurements of the ARA is, however, questioned by many authors. The main drawback of the method is inability to differentiate the effect of pelvic floor laxity from the incontinence on the basis of ARA result.³

Many clinicians continue, however, to place credence in the ARA, and routine measurements are often taken.³ This examination, apart from estimating ARA, allows physicians to evaluate the efficiency of rectal sphincters, pelvis floor muscles and susceptibility of the rectal ampulla. It is at this time probably the only objective means of measurement of anorectal anatomy and function because the sitting position for examination is not easily attainable with other methods.⁷

Defecography was first described in 1952 by Walden.⁸ In 1953 Ekengren and Snellman⁹ published an article in which they presented the application of defecography in diagnostics of constipation. In 1968 Broden and Snellman¹⁰ characterized and named the defecographic technique as well as indications for its application. In 1980s Mahieu *et al.*^{11,12} described the application of defecography as a new diagnostic procedure. Their work consisted of two parts and included an evaluation of anorectal functions using defecography. The investigation was carried out on healthy patients and patients suffering from proctologic diseases.

We present results of defecography per-

formed in several groups of patients with following disorders:

- constipation,
- sensation of obstruction or incomplete defecation,
- suspicion of rectocele,
- faecal incontinence,
- rectal prolapse.

Defecography turned out to be a useful examination and allowed for a very precise diagnosis. In a group of patients with the sensation of incomplete defecation and sensation of obstruction, for example, six out of thirteen were diagnosed with rectocele. It was also possible to measure ARA fairly precisely and in this way to evaluate the function of the pelvic diaphragm what is impossible using other diagnostic methods. Abnormal values of ARA were detected in the group of patients characterized by constipations, faecal incontinence and the sensation of obstruction in the rectum. It could be related to defective function of pelvic diaphragm and in some cases with the low contractility of puborectal muscle. Signs of nonrelaxing puborectalis muscle Agachan *et al.*¹³ found in 28.8% of the patients with defecatory disorders. He used manometry, electromyography, and defecography. The latter in his opinion was probably the best for this purpose. This opinion is supported by Karasics *et al.*,¹⁴ who claims that the value of the ARA is directly dependent on the puborectal muscle activity. Not effective contraction of the puborectalis causes abnormal values of the ARA in each phases of defecation. He adds that many patients have not evident functional diseases of the rectum which may be diagnosed by means of defecography. Also Jorge *et al.*,³ who compared defecography with proctography, found defecography reliable and superior, mostly because it is the only diagnostic test which provides anatomic details.

In the majority of our patients suffering from incontinency value of the ARA was abnormal. Almost half of them had the exces-

sive lowering of the pelvis floor, which might have led to incontinency. The latter factor is underlined by many authors.³

ARA did not turn out to be characteristic for patients with rectal prolapse. Although the defecographic examination was difficult to carry out in this group of patients, it showed the mechanism of rectal prolapse and was useful in choosing the right surgery technique. Defecography is particularly useful in the diagnostics of early stages of the rectal prolapse when the upper part of the rectum becomes intussuscepted. In one case we observed acute ARA during the maximal sphincters contraction following the rectocele surgery because of the rectal prolapse, which was typical for the functional results of surgery of that type.

Defecography has also proved to be effective in the evaluation of patients who suffered from solitary ulcer of rectum. During the examination of these patients it has been observed that ARA in various phases of defecation has flattened. The duration of sphincter relaxation in the studied group was changeable and did not depend on the kind of pathology.

Despite improvements in imaging technique and better understanding of anorectal disorders, the exact role of defecography in defining anorectal disorders and its impact on therapy remains controversial.^{7,14} In spite of its undoubted diagnostic value we conclude that this examination should be an additional one to the clinical examination. The defecography is enable to visualise the peritoneal outline and its pouches, and may be of limited value in case of enterocele or rectal intussusception¹⁶ (although in the latter, defecography is necessary to sort out cases of intussusception that might be clinical relevant whereas the clinical diagnosis of intussusception is related only to long intussusception).¹⁷ The problem may also result from e.g. multifactoral aetiology of obstructed defecation which makes it difficult to determine whether de-

fecographic findings are the cause or result of excessive straining in patients with the obstructed defecation.⁷ Additionally, there are scientific works which describe healthy volunteers who underwent this examination. Although they had not suffered from any proctological ailments, the defecographic examination detected some disorders.

Besides, not all the parameters which were used in our study appeared reliable for other researchers. Klauser¹⁸ tested reproducibility and agreement among three clinicians (a radiologist, a gastroenterologist, and a colorectal surgeon), all experienced in defecography, in evaluating defecographies, and did not include in his study the measurement of the ARA. In his opinion, it has no clinical relevance. Dvorkin *et al.*¹⁹ compared magnetic resonance defecography and evacuation proctography. They confirmed the primary role of proctography for the diagnosis of intussusception, and the complementary role of magnetic resonance defecography by giving information on movements of the whole pelvic floor. Whereas Beer-Gabel *et al.*²⁰ found no differences between dynamic transperineal ultrasound and defecating proctography for the measurement of the ARA, anorectal junction position at rest and during straining.

Although defecography cannot be the only grounds for treating the patient,⁷ contemporary surgery of large intestine should be supplemented with a detailed evaluation of rectum functional functions. Our results in several case-series presented did not allow for any definitive data because of the heterogeneity of the included group. They are preliminary, and some cases, e.g. solitary rectal ulcer and rectal prolapse, were presented due to their rareness. The whole work will continue but at this stage we are convinced that defecography is one of the examinations which can be helpful in the evaluation of patient's motor functions both before and after the operation.

Conclusions

1. Abnormal values of Parks' angle at rest and during constipation were detected at patients who suffered from: faecal incontinence, sensation of obstruction in rectum and with constipation.
2. Values of Parks' angle did not turn out to be characteristic for the examined group of patients with rectal prolapse.
3. Duration of sphincter relaxation was individually variable and did not depend on the pathology.
4. Defecography enabled to detect concomitant rectocele at patients with constipations and the sensation of obstruction in rectum
5. Defecography was helpful at the evaluation of patients with solitary ulcer of rectum. In these cases ARA at various stages of defecation becomes "more flat".

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case report

Lhermitte-Duclos disease and pregnancy

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Background. Lhermitte-Duclos disease or dysplastic gangliocytoma of the cerebellum is a rare disorder that can cause progressive mass effects to the structures occupying posterior fossa. Magnetic resonance imaging is a diagnostic modality of choice demonstrating characteristic non-enhancing gyriform pattern with the enlargement of cerebellar folia, hypointense on T1 and hyperintense on T2 weighted magnetic resonance images.

Case report. The authors present a case of 37-year old woman with previously unknown Lhermitte-Duclos disease in the third trimester of pregnancy from the first signs of the disease to the first six months after delivery.

Conclusions. More experience will be needed with this disease in pregnancy and post delivery period to recommend pregnancy for women with such condition. However, this case shows that a pregnant woman with Lhermitte-Duclos disease could reach full-term pregnancy and deliver a healthy child, without life-threatening risk.

Key words: cerebellar neoplasms; ganglioneuroma

Introduction

Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) is a rare disorder, characterized by a slowly progressive unilateral neoplastic mass of the cerebellar cortex. The histopathological findings of Lhermitte-Duclos disease (LDD) include the widening of

the molecular layer, which is occupied by abnormal ganglion cells, absence of the Purkinje cell layer and hypertrophy of the granular cell layer. Magnetic resonance imaging (MRI) is a diagnostic modality of choice and reveals a characteristic non-enhancing gyriform pattern with the enlargement of cerebellar folia. The lesion is hypointense on T1- and hyperintense on T2-weighted magnetic resonance images.¹ In patients with a posterior fossa tumour suggestive of a dysplastic gangliocytoma on neuroimaging studies, a pathologic confirmation is necessary.²

Dysplastic cerebellar gangliocytoma is commonly associated with the progressive mass effect in the posterior fossa and is typi-

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cally presented with headaches, cerebellar dysfunction, occlusive hydrocephalus and cranial nerve palsies. The disease usually manifests in young adults, but the age at presentation ranges from birth to the sixth decade. There is no sex predilection. The therapy consists of decompression of the posterior fossa by a total surgical removal of the tumour mass.³ A problem of surgical removal of these tumours is to miss the borderline between tumour and healthy cerebellum tissue so that the incomplete removal of the tumour is not rare.⁴

To our knowledge there were no reports of LDD in pregnancy. In our case report we intend to present the potential influence of LDD on pregnancy and delivery.

Case report

A 37-year-old woman was admitted at the Clinic of Gynaecology and Obstetrics in the 27th week of her first pregnancy for monitoring and programming the childbirth. Hospitalisation and programmed delivery by caesarean section has been recommended from her neurosurgeon before the control MRI was preformed, because she had a history of partial cerebellar tumour resection. Namely, 19 years ago, CT was performed due to the cerebellar dysfunction and the increased intracranial pressure (intensive headaches, nausea, dizziness and optical nerve oedema). CT had shown a large mass of the right cerebellar hemisphere suspicious of gliomal tumour and she underwent the neurosurgical extirpation. Only a partial resection was preformed with the implantation of ventriculoatrial shunt. The histopatological findings included a widening of cerebellar cortex due to hypercellular granular layer without a clear border with thin molecular layer and presence of large Purkinje cells. The presence of true neoplastic tissue was not found and regular CT controls were recom-

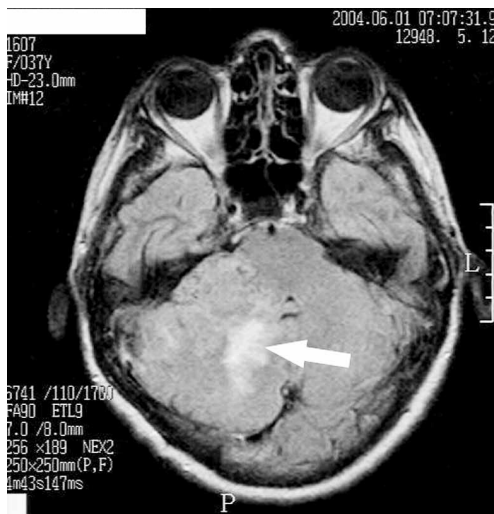


Figure 1. Axial FLAIR-weighted image (IR, 6741/110/1700) reveals ill-defined area of the increased signal intensity occupying the right cerebellar hemisphere with perifocal white matter oedema (arrow).

mended. She constantly suffered from headache and dizziness in exertion when she had the opportunity to do MRI eight years ago. After this first MRI which described tumourous mass in the pontocerebellar angle and the right cerebellar hemisphere, a new resection with drainage was recommended when she was 29-years old, but our patient did not accept surgery. The symptoms were stable during pregnancy when in the third trimester became more frequent and aggravated. The neurosurgeon recommended MRI before making decision for the route of child delivery. MRI was performed in the 29th week of pregnancy showing the expansive lesion of the right cerebellar hemisphere with characteristic features (Figures 1 and 2).

Nineteen years from her first symptoms our radiologist, based on typical MRI findings and history, concluded that it must have been Lhermitte-Duclos disease. The neurosurgeon recommended delivery by caesarean section and our patient delivered a healthy male child after 40 weeks of pregnancy. After delivery she reported the aggravation of symptoms: headache, dizziness, disturbance of balance



Figure 2. Coronal T2-weighted image (SE 4350/88) shows a large mass in the right cerebellar hemisphere with the incomplete distortion of the cerebellar folia (arrowhead).

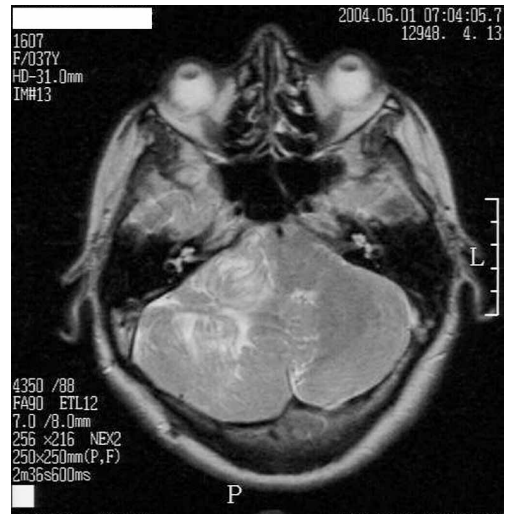


Figure 3. Axial T2-weighted image (SE 4350/88) demonstrates a typical "tiger-striped" pattern of the lesion with compression of the fourth ventricle.

and paresthesia in both arms. She suffered from this discomforts for six months when she went on control MRI. Control MRI was unchanged, but she accepted the operation at that time. Pathohistological findings confirmed our radiological diagnosis.

Discussion

Tumours of ganglion cells are very rare. They include: gangliocytoma, ganglioneurinoma, Lhermitte-Duclos disease and dysembryoplastic neuroepithelial tumour. Some considered them to be dysplasias rather than true neoplasm; others refer to them as malformations.⁵ Lhermitte-Duclos disease is a rare cerebellar lesion with features of both malformation and benign neoplasm. MR imaging usually distinguishes the LDD by its characteristic "tiger-striped" appearance (Figure 3).⁶

In recent years several cases involving the association between LDD and Cowden's syndrome (CS), an autosomal dominant condition characterized by multiple hamartomas and neoplastic lesions in the skin and inter-

nal organs were reported. These included mucocutaneous lesions, acral keratosis, thyroid adenoma, fibrocystic disease ovarian cyst, intestinal polyposis, and arteriovenous malformation. Patients with LDD should receive a complete dermatological and systemic screening, because some of the lesions can develop into malignant tumors.⁷ The association between Lhermitte-Duclos disease and Cowden disease has been under-recognized and under-reported. The recognition of this association has a direct clinical relevance because a diligent long-term follow up monitoring of individuals with Lhermitte-Duclos disease and Cowden disease may lead to the early detection of malignancy.⁸ In approximately 40% of documented cases of LDD, CS can be diagnosed, and in 60% of cases LDD appears to occur sporadically.⁹ Patients diagnosed with Lhermitte-Duclos disease must be adequately evaluated for Cowden's syndrome.¹⁰

We presented a 37-year-old pregnant woman who had an isolated form of LDD beginning in her teenage period (16 years). During pregnancy she was under the permanent supervision of her obstetrician and no

obstetric complications were obtained. Pregnancy is an aggravating factor for brain tumours acting by three mechanisms: acceleration of tumour growth, increase of peritumoral oedema and development of immunotolerance to foreign tissue agents. There may be a relation between pregnancy hormones. According to Depret-Mosser *et al.*¹¹ induced therapeutic abortion and caesarean section are no longer routinely performed, and now being replaced by vaginal delivery with a systematic instrumental extraction. The presence of an intracranial neoplasm during pregnancy has a serious implication for the anaesthetic management of labour and delivery. The physiological changes of pregnancy and labour are potentially hazardous to women with intracranial neoplasm, but the provision of adequate pain relief during labour reduces the risk for the mother.¹² The other group of authors recommended caesarean delivery with the patient under general anaesthesia, followed by the immediate neurosurgical decompression in neurologically unstable patients to minimize temporal lobe or cerebellar herniation.¹³ The delivery should be advocated in the early third trimester after documentation of foetal pulmonary maturity. In our case we had a neurologically stable patient who reached the full term pregnancy. The obstetrician took into consideration her age (37 years), reported deterioration of symptoms in exertion and recommended neurosurgical examination before making his decision for elective caesarean delivery.

The way of delivery is still a question and should be solved between the obstetrician and the neurosurgeon for each patient individually. More experience with LDD in pregnancy is necessary for making a solid attitude about a way of delivery in neurologically stable patients. The management of brain tumours should be tailored to the individual patient. There may be a relation between pregnancy hormones and the rate of brain tumour growth mediated through specific intracellular receptors.¹⁴

More experience will be needed with this disease in pregnancy and post delivery period to recommend pregnancy for women with this condition. However, this case shows that a pregnant woman with LDD could reach full-term pregnancy and deliver a healthy child, without serious risk for her life.

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Locoregional control and survival after breast conserving therapy

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Background. The purpose of our study was to present a 5-year survival and locoregional control rates in breast cancer patients and to establish eventual impact of the treatment and patient characteristics on locoregional control and survival.

Methods. From January 1998 to December 1999 564 stage 1 and 2 breast cancer patients were treated with breast conserving therapy. We evaluated the following characteristics: age, histological diagnosis, grade, size, number of metastatic lymph nodes, hormonal receptor status, extensive intraductal component (EIDC), vascular invasion, pathologic tumour margins, type of surgery and use of adjuvant therapy.

Results. The mean age of our patients was 54.2 years. Invasive ductal carcinoma was the most common diagnosis (82.4%), followed by invasive lobular carcinoma (10.6%). Most of the tumours were grade 2. Seventy-two % of patients had T1 tumours, 24% T2 and 3% T_{is} tumours. Metastatic lymph nodes were present in 44% of patients. All patients were treated with breast conserving surgery followed by radiotherapy (RT). Fifty % of patients received adjuvant chemotherapy and/ or hormonal therapy. The 5-year survival rate was 88.5%. Tumour size, number of metastatic lymph nodes, grade, hormonal receptors and vascular invasion proved to be statistically significant prognostic factors for the survival, while age and histological diagnosis were not. Local recurrence developed in 4.3% of our patients, while in 3.4% regional recurrence developed.

Conclusions. Breast conserving surgery followed by RT was associated with good rates of locoregional control and survival, comparable to those reported in the literature.

Key words: breast neoplasms – surgery; survival analysis

Introduction

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Breast conserving therapy has been used since the 1960s and is now considered best practice in the treatment of early breast cancer. Retrospective and prospective randomized trials demonstrated that breast conserving therapy (BCT) produces rates of survival

and locoregional control similar to those of mastectomy.¹ Breast conserving surgery removes a detectable disease in the breast and/or regional lymph nodes, but has no effect on possible undetected disease in the remaining breast, chest wall, regional lymph nodes or distant sites.² By combining surgery, radiotherapy and adjuvant systemic therapy we can lower the risk of locoregional and distant recurrence.

In spite of this combined therapy there are still patients who develop recurrences. Local recurrence rates of 5-20% have been reported in different studies after BCT.¹⁻³ Although the impact of local recurrence on overall survival is not well established, it has a detrimental psychological effect on the patient.^{1,4,5} By identifying those patients who have higher risk of developing a locoregional and/or distant recurrence, we can determine the right treatment to minimize the risk.¹

The purpose of this retrospective study was twofold. First of all, to present a 5-year survival and locoregional control rates in patients treated at Institute of Oncology in Ljubljana and, secondly, to establish the eventual impact of treatment and patient characteristics on locoregional control and survival.

Methods

From January 1998 to December 1999 564 breast cancer patients stage I and II were treated at the Institute of Oncology Ljubljana with breast conserving therapy. The patient data were obtained by medical records. We evaluated the following patient and tumour characteristics: age, histological diagnosis, grade, size, number of metastatic lymph nodes, hormonal receptor status, extensive intraductal component (EIC), vascular invasion, pathologic tumour margins, type of surgery and use of adjuvant therapy. We recorded eventual locoregional and/or distant recurrence by the retrospective analysis.

Statistical univariate analyses were done using the SPSS program. A statistical significance was assessed with Log-rank, Breslow and Tarone-Ware tests.

Results

Patient and tumour characteristics

The patient's age ranged from 28 to 77 years. The mean age was 54.2 years. The age distribution is presented on the histogram (Figure 1).

Most of the tumours were present in the upper outer quadrant (45%), followed by the outer lower quadrant (11%). Invasive ductal carcinoma (IDC) was by far the most common histological diagnosis (82.4% of tumours), followed by invasive lobular carcinoma (ILC) (10.6%) and ductal carcinoma in situ (DCIS) (2.6%). Other histological types of tumours were rare. The grade was more evenly distributed. The most common was Grade 2 with 44%, followed by Grade 3 with 33% and Grade 1 with close to 26%.

Most of the tumours were T1 (72%) and T2 (42%). Tis was present in 3% of cases. Sixty-six % of patients had negative axillary lymph nodes, 25.7% had one to three metastatic lymph nodes and 7.6% had more than three metastatic nodes.

Positive estrogen receptors were detected in 66.4% of tumours and positive progesterone

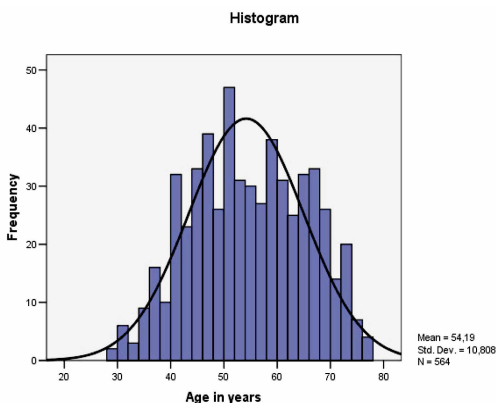


Figure 1. Age distribution of the patients.

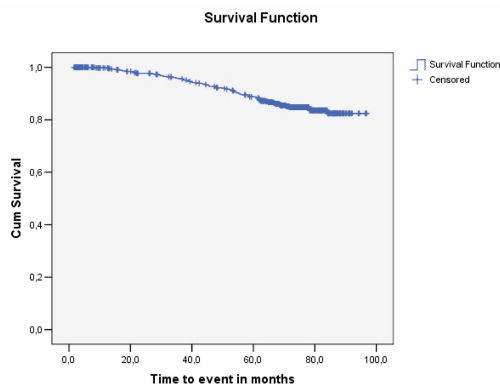


Figure 2. Overall survival of patients.

terone receptors in 51.1%. Vascular invasion was present in 2.6% of tumours and 15% of tumours had an EIDC.

Treatment

All patients were treated with breast conserving operation, either tumorectomy or quadrantectomy. All patients received postoperative radiotherapy with two tangential fields. The total dose was 50 Gy followed by a boost with electrons to the tumour bed of 10 to 16 Gy. In patients with more than three metastatic axillary lymph nodes, 50 Gy was given to the supraclavicular fossa. No patient received radiotherapy to the axilla. About half of patients received adjuvant chemotherapy (54%) and hormonal therapy (50.4%).

Survival

The 5-year overall survival rate was 88.5% (Figure 2).

Prognostic factors for survival

In the context of our analysis, age and histology proved statistically non significant, while the influence of tumour size, nodes, grade, estrogen and progesterone receptors, vascular invasion and local and regional failure was significant.

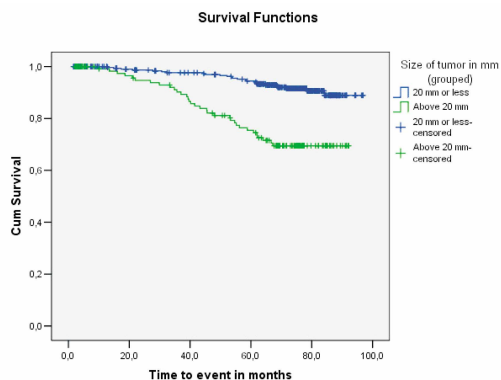


Figure 3. Impact of the tumour size on survival ($p = 0.000$).

As expected, a larger tumour leads to a lower survival probability (Figure 3). In this case as well as in other presented graphs, that will follow, the difference was statistically significant.

Comparing the overall survival rate (88.5%), in patients with Grade 3 tumours it was well below 80%, while for the patients with Grade 1 tumours it was close to 100% (Figure 4).

The patients who had tumours with positive estrogen and progesterone receptors had higher survival probability (Figures 5, 6).

The patients with a local recurrence had lower survival probability (Figure 7). The same holds for regional recurrence (Figure 8). For these patients the 5-year survival was just above 20%.

Vascular invasion proved to be a statistically significant prognostic factor. For patients with tumours with vascular invasion, the 5-year survival was just above 20%. We have to mention the problem of missing data for this particular prognostic factor, so we should be careful when interpreting the results.

Prognostic factors for local recurrence

The local recurrence occurred in 4.3 % of patients. Since the number of cases with local recurrence was small we used a simple cross-tabulation analysis (Table 1).

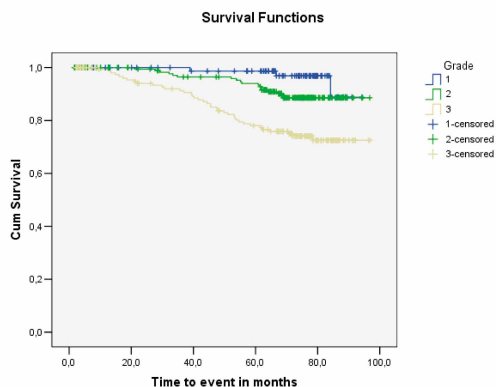


Figure 4. Impact of the tumour grade on survival ($p = 0.000$).

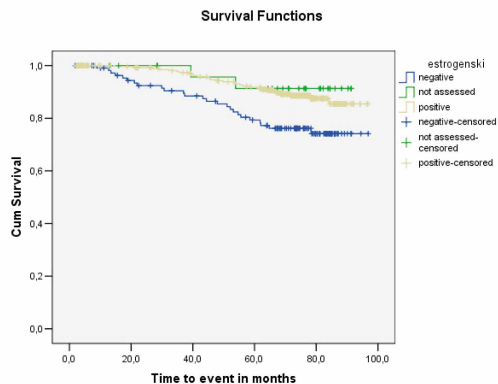


Figure 5. Impact of the tumour estrogen receptors on survival ($p = 0.004$).

Tumour grade, number of metastatic lymph nodes, surgical margins and hormonal receptors were prognostic factors for development of local recurrence.

Prognostic factors for regional recurrence

The regional recurrence occurred in 3.4% of patients. The total number of recurrences was 19. The total number of patients with metastatic axillary lymph nodes was 188. One recurrence was in the axilla, one in the parasternal region and 17 in the supraclavicular region (Table 2).

The small number of events is a problem for statistical analysis. However, the number of metastatic lymph nodes in the axilla is a risk factor for supraclavicular recurrence in our patients.

Discussion

In the study we tried to evaluate the 5-year survival and locoregional control in our patients after BCT and to establish eventual prognostic factors. The overall 5-year survival was 88.5%. This result is similar to other studies.¹ Prognostic factors that had an impact on the survival were tumour size, nodes, grade, estrogen and progesterone receptors, vascular invasion and local and regional failure.

As expected, larger tumours led to lower survival probability. There was a marked difference between tumours with diameter less than 2 cm compared to those with more than 2 cm (90% versus 70% 5-year survival).

There was also a marked difference regarding the tumour grade with lesser survival

Table 1. Prognostic factors for local recurrence

Prognostic factor	% of Local recurrence
Grade	Grade 1 – 1.8%
	Grade 2 – 3.6%
	Grade 3 – 7.8%
Number of metastatic axillary lymph nodes	0 – 2.7%
	<3 – 5.5%
	>3 – 14%
Margins	Free margins – 2.7%
	Involved – 12.5%
Estrogen, progesterone	Negative receptors → higher chance of local relapse

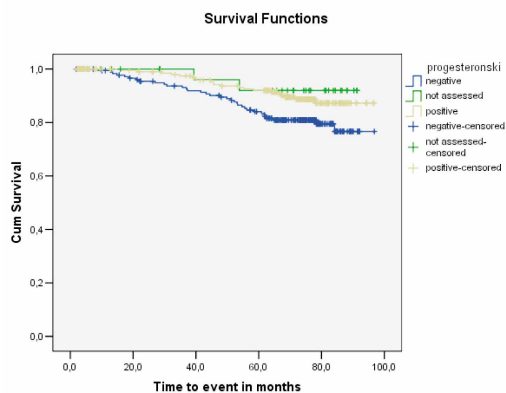


Figure 6. Impact of the tumour progesterone receptors on survival ($p=0.03$).

probability in patients with less differentiated tumours.

The number of metastatic axillary lymph nodes is a well established prognostic factor² which was also confirmed in our study. Patients with negative lymph nodes had 90% 5-year survival probability, while those with more than three metastatic nodes had only 40%.

The presence or absence of hormone receptors had also an impact on the survival. Those patients who had positive receptors had higher survival probability. The same is true for patients who had tumours without vascular invasion. We have to mention that a lot of data was missing for this variable, so we

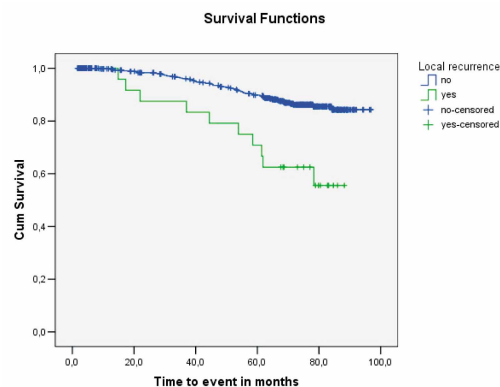


Figure 7. Impact of the tumour local recurrence on survival ($p=0,000$).

Table 2. Number of metastatic lymph nodes and percentage of regional recurrence

No of metastatic lymph nodes	% of regional recurrence
0	1.6
1-3	6.3
>3	9

can not be conclusive regarding this prognostic factor.

Local and regional failure influenced the survival. A recent meta-analysis confirmed the impact of local recurrence after BCT on survival which is similar to the impact of a recurrence after modified radical mastectomy. It is estimated that for 4 local relapses avoided 1 life will be saved.^{1,2,6}

Interestingly, age was not a significant prognostic factor for the survival.

The local recurrence occurred in 4.3% of patients. This is comparable to other studies, where the local failure ranges from 1.2-20%.^{1,7-9}

We tried to identify the prognostic factors for local recurrence, but the small number of patients with local recurrences made the analysis difficult. We found some impact of grade (higher grade, more recurrences), number of metastatic lymph nodes (more metastatic lymph nodes, more relapses), surgical resection (patients with involved margins had

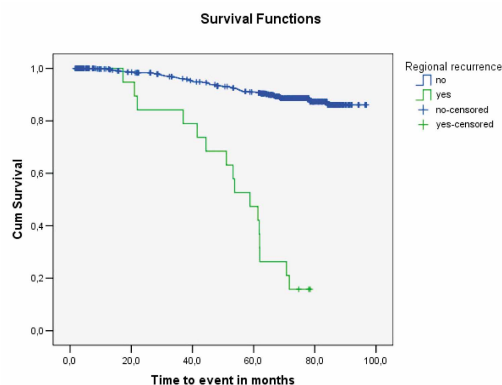


Figure 8. Impact of the tumour regional recurrence on survival ($p=0,000$).

more local recurrences) and the receptor status (positive receptors, better prognosis).

The regional recurrence was less common, with 3.4% of patients. Most of the regional recurrences developed in the supraclavicular fossa and only one in the axilla.

Therefore we conclude that there is no need to irradiate the axilla after an axillary dissection even if metastatic lymph nodes were found at the operation.

Conclusions

Survival and locoregional control rates in our patients are comparable to those reported in the literature. Axillary recurrence is rare after an axillary dissection even in patients with >3 metastatic lymph nodes without RT to the axilla.

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case report

Neck extensor muscle weakness (Dropped head syndrome) following radiotherapy

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Background. Dropped head syndrome is an unusual condition in which the head cannot be held upright in its normal anatomic position secondary to pronounced, isolated, neck extensor muscle weakness.

Case report. A case of dropped head syndrome in a female with a history of radiotherapy for Hodgkin's lymphoma and a clinical history consistent with multiple sclerosis is presented, and potential etiologies are discussed.

Conclusions. Muscular atrophy and lower motor neuron injury secondary to isolated anterior horn cell injury from radiotherapy emerge as the most likely etiology.

Key words: Hodgkin disease - radiotherapy; muscular atrophy; muscle weakness; head

Introduction

Dropped head syndrome, a result of neck extensor weakness, is a rare but striking clinical entity. Patients with this condition experience significant neck muscle weakness that leads to an inability to elevate the head from the chest. Our report presents a case of a woman with a clinical history of probable multiple sclerosis (MS) who developed dropped head syndrome after sequential courses of thoracic and cervical spine irradiation ten years apart.

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Case report

In 1972 a 46 year old female presented with mild, intermittent symptoms of diplopia, dysarthria, fatigue, ataxia, and incoordination and was subsequently diagnosed with probable multiple sclerosis on clinical grounds by an experienced neurologist at our institution. She had mild neurological deficits from approximately 1972 to 1995, corresponding to an Eastern Cooperative Oncology Group/Zubrod performance status of 1, with minimal relapses and no history to suggest transformation to secondary progressive MS. Her past medical history was otherwise unremarkable, although she had received four fractions of radiation therapy to the left wrist for a possible fracture of the pisiform bone in the 1940's.

In 1975, the patient presented with in-

guinal adenopathy and a biopsy revealed mixed cellularity Hodgkin's lymphoma (MCHL). Her clinical stage was IIA, with involvement of inguinal and external iliac adenopathy. She received treatment to the pelvis and para-aortic lymph nodes with radiotherapy using an "inverted Y-technique." Approximately one year later, a chest x-ray revealed right hilar adenopathy. Salvage radiotherapy was instituted. She was treated with radiotherapy alone to a modified mantle radiotherapy field that also included the entire volume of both lungs to a dose of approximately 18 Gy followed by treatment to a traditional mantle field to a total central axis dose of 33 Gy. The dose delivered to the cervical spinal cord from the C3 to C7 vertebral bodies was approximately 31.1 Gy in 16 fractions.

The patient developed a pathologically confirmed recurrence of MCHL ten years later, in 1986, in the right parotid gland. Treatment was once more in the form of radiotherapy alone, to dose of 36 to 44 Gy. Opposed lateral 6 MV photon beams were used to treat a field encompassing the neck and Waldeyer's Ring, with 9 MeV electron beams being employed over the spinal cord to limit the maximum spinal cord dose in the cervical region to 9 Gy in 20 fractions. Assuming no unintended overlap of the matched radiotherapy fields, the total cervical spinal cord dose for all radiotherapy was approximately 41 Gy. She received no other therapy.

There was no evidence of MS exacerbation or any other change in neurological function during or immediately after either course of radiotherapy. In 1995, the patient developed progressive neck extensor weakness resulting in an inability to hold her head upright. A detailed exam by her neurologist demonstrated new symmetrical, isolated neck extensor weakness with accompanying muscle atrophy. The neurological exam otherwise showed no changes in her chronic deficits consisting of a mild mixed spastic ataxic gait and mild

dysarthria, which were presumed secondary to MS. A provisional diagnosis of "dropped head" or "floppy neck" syndrome was made. At presentation, the neck weakness was mild, but became progressively more severe, resulting in an inability to hold her head upright without assistance over the next year. A Tensilon test was negative for myasthenia gravis. She never developed evidence of myelopathy over ten years of observation. However, over the last few years she has developed progressive dysphagia seemingly related to a combination of her baseline deficits, the severely flexed position of her head, and progressive bulbar weakness, eventually requiring initiation of gastrostomy tube feedings. We wondered if perhaps this weakness was in part related to the same process affecting her cervical segments given the likely exposure of her brainstem to radiotherapy when the localized parotid recurrence was treated. Unfortunately, the patient never had an EMG (electromyography) or magnetic resonance imaging (MRI) of her spinal axis to better define her condition. However, clinically, she has not developed signs of more widespread motor neuron disease, paraneoplastic syndrome, or more widespread central nervous system demyelination.

The patient currently remains alive, free of recurrence of Hodgkin's lymphoma (HL), but debilitated by age, multiple medical comorbidities, and dropped head syndrome. Aggressive interventions are being avoided and testing declined. Her neck extensor weakness has been managed with a soft cervical collar.

Discussion

Floppy head syndrome, also commonly referred to as "dropped head syndrome", is the result of isolated weakness of the neck extensor muscles, without evidence for a more widespread neuromuscular disorder. This syndrome is characterized by an inability of

patients to elevate the chin from the chest, resulting in difficulty swallowing, speaking and breathing. Differential diagnosis for neck extensor muscle weakness includes myasthenia gravis, a variety of primary myopathies, amyotrophic lateral sclerosis, hypothyroidism, and disorders of the spine.¹⁻³ It has been rarely been described as a late effect of external beam radiotherapy treatment, primarily following treatment of Hodgkin's lymphoma.⁴

In the current case, the etiological considerations are influenced by the occurrence of multiple courses of radiotherapy, and a pre-existing neurological disorder which on the basis of history and examination in the pre MRI era was thought to be consistent with MS. Diagnostic considerations include 1) chronic progressive radiation myelopathy, 2) progression of the underlying chronic neurological illness, 3) muscle atrophy secondary to radiotherapy, 4) selective cervical segment anterior horn cell injury specifically related to radiotherapy, or 5) neuromuscular disease unrelated to MS or radiotherapy but with predominant involvement of neck extensor muscles.

This patient did not evolve the typical clinical findings of chronic, progressive, transverse radiation myelopathy. Reagen *et al.* described four manifestations of radiation induced myelopathy in 1969.⁵ The first syndrome is that of a transient myelopathy, mostly manifesting Lhermitte's symptom and other sensory disturbances. The second syndrome manifests with rapidly evolving paraplegia or quadriplegia as a result of spinal cord infarction. The third syndrome of radiation myelopathy involves selective damage to anterior horn cells, resulting in limited distribution lower motor neuron disease. The fourth form manifests as a chronic progressive myelopathy. Typical symptoms of chronic progressive radiation myelopathy include pronounced sensory loss as well as weakness at all levels below the area of injured spinal

cord. Patients experience sensory changes, particularly in the lower extremities, hyperreflexia and other symptoms of spasticity, and bowel and bladder dysfunction. In our case, the patient exhibited only isolated neck extensor muscle weakness in the absence of sensory or reflex changes, making it unlikely that cord infarction or chronic progressive myelopathy were the etiology of her neurological dysfunction.

A second explanation for the patient's dropped head syndrome would be progression of her previously noted neurological illness, provisionally MS, as offered by an experienced Mayo Clinic neurologist before the era of MRI. An additional consideration in this regard would be the effect of irradiation on the spinal cord in a patient with MS. Although an increased risk of neurotoxicity in MS patients receiving spinal cord radiotherapy has not been reported in the medical literature, anecdotal cases of dramatic toxicity after brain irradiation have been published.⁶ Though demyelination in the spinal cord can be associated with significant lower motor neuron dysfunction in the segments affected, additional signs of myelopathy are almost always apparent. It is noteworthy that this patient never developed any additional clinical evidence for more widespread central nervous system demyelination, including other signs of progressive spinal cord dysfunction. Whether or not the presence of an underlying demyelinating disorder played any role in the appearance of dropped head syndrome in this patient could not be determined.

Gradual atrophy and lack of development of bone and muscle in children and adolescents following radiotherapy has been well documented.⁷ Adult survivors of HL also report neck and shoulder symptoms, although the effects of irradiation of adult muscles and bones shows markedly less effect than is typically seen in children whose musculoskeletal systems are still not fully matured.⁸ Portlock

et al. have reported a case of dropped head syndrome following Mantle irradiation for HL in which muscle biopsies confirmed the presence of non-inflammatory, nemaline myopathy within the radiation treated area and its absence outside the treated region. Nemaline myopathy unrelated to radiotherapy has also been associated with dropped head syndrome.⁹

Though an isolated neck extensor myopathy due to radiotherapy cannot be excluded, we feel that the most likely explanation for this patient's neck extensor weakness is lower motor neuron dysfunction secondary to radiation toxicity in anterior horn cells of the cervical spinal cord. Sporadic case reports, beginning in 1948, have appeared in the medical literature describing a clinical picture of "isolated motor symptoms, amyotrophy, paresis, and fasciculations" resulting from radiation injury to anterior horn cells of the spinal and/or the most proximal segment of peripheral nerves.¹⁰ The majority of cases have followed treatment of testicular neoplasms, resulting in lumbar lower motor neuron (LMN) disease, but some reports have described cervical LMN injury after irradiation of the cervical spine.¹¹ Esik has provided a tabular review of 47 published cases of this syndrome and drawn parallels between this form of radiation injury and LMN injury following viral infections. Although agreement does not exist in the medical literature regarding the underlying mechanism of injury, LMN disease typically follows radiotherapy at doses lower than the typical threshold for chronic progressive radiation myelopathy, 45 Gy, and has been reported occurring in a number of cases below a dose of 30 Gy.¹²

Dropped head syndrome can be a potentially debilitating disease, resulting in dysphagia, dyspnea, and traction injury of the spinal cord in severe cases, especially in an older individual with advanced cervical spondylosis. In evaluating patients with newly diagnosed, isolated neck extensor weak-

ness, potentially treatable neuromuscular disorders should be first considered and excluded. In the current case, differentiation between the two most probable etiologies, a direct myopathic radiation injury versus muscle weakness secondary to LMN from anterior horn cell injury, was problematic as the patient declined an aggressive investigative approach. Cervical MRI, EMG, muscle biopsy and laboratory investigation might have provided a more definitive diagnosis.

In patients with neck extensor weakness, after elimination of potentially treatable disorders, care is primarily supportive. A collar or brace should be considered to provide support for the head in a more anatomically normal position to facilitate activities of daily living and to help prevent contractures of the neck in a fixed flexed posture. Investigational therapies for dropped head syndrome with immunoglobulin and surgery have been reported in case form.^{13,14}

Isolated neck extensor weakness appears to be a rare complication of radiotherapy. This case highlights the selective vulnerability of muscle, motor neurons, or both to radiation, and the need to consider the potential relevance of concurrent neurological or neuromuscular disease in the manifestation of this disabling condition.

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case report

Ameloblastic fibroma

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Background. Ameloblastic fibroma (AF) is a rare odontogenic tumour. It consists of odontogenic ectomesenchyme resembling the dental papilla and epithelium resembling dental lamina and enamel organ without dental hard tissues.

Case report. A case report of a large ameloblastic fibroma involving the body of mandible from the lower left second incisor (32) to the lower left second molar (37) is presented. To our knowledge this is the only case of ameloblastic fibroma reported from Slovenia.

Conclusions. An aggressive surgical treatment is suggested because of the possibility of recurrence and the possibility of malignant transformation of an AF to an ameloblastic fibrosarcoma.

Key words: fibroma; odontoma; mandibula neoplasms

Introduction

Despite Ameloblastic fibroma (AF) is a rare odontogenic tumour, it occurs predominantly in children and therefore remain an important diagnostic consideration.¹ It usually arises from the mandibular dentition although it can arise in maxilla.²

AF consists of odontogenic ectomesenchyme resembling the dental papilla and epithelium resembling dental lamina and

enamel organ without dental hard tissues.³ Knowledge of the malignant potential in the mesenchymal spindle cells of AF should assist in determining the management of these benign tumours, and may prevent malignant transformation to ameloblastic fibrosarcoma.⁴

At the Clinical Department of Maxillofacial and Oral Surgery in Ljubljana this is the only case of this tumour and to our knowledge the only one in Slovenia. Table 1 presents the frequency of odontogenic tumours from June 1995 to June 2005.

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Case report

A 23-years old Caucasian asymptomatic woman visited her dentist in March 2004. On dental panoramic tomogram (DPT) a radiolucent lesion formed from three separate com-

Table 1. Odontogenic tumours seen at the Clinical Department of Maxillofacial and Oral Surgery in Ljubljana, Slovenia from June 1995 to June 2005.

Tumour	Number of cases	Relative frequency among odontogenic tumours (%)
Ameloblastoma	20	35.1
Odontogenic myxoma	3	5.3
Ameloblastic fibroma	1	1.8
Adenomatoid odontogenic tumour	2	3.5
Ameloblastic Fibrodentinoma	1	1.8
Cementoma	1	1.8
Odontogenic Fibroma (peripheral)	4	7.0
Calcifying Odontogenic Cyst	4	7.0
Complex Odontoma	21	36.8
Total	57	100

partments from the region 32 to 36 was found (Figure 1A). In February 2005 another DPT showed the lesion had increased. The roots of the teeth 35 and 36 were resorbed. The lesion was presumed to be a cyst so she was not sent to a maxillofacial surgeon before May 2005.

The patient's family anamnesis was positive for neoplasms, diabetes and coronary heart disease. Her brother has Down's syndrome.

A large hard swelling under intact soft tissues was palpated in the lower left vestibulum, all teeth were vital.

A pathohistologic examination showed strands of odontogenic epithelium. In the centre the cells were focally similar to the embryonic stellate reticulum. The epithelial islands were surrounded by a rich mesenchymal component reminiscent of the dental papilla cells. Rare mitoses were present and the nuclear polymorphism was minimally expressed.

The teeth 31, 32, 33 and 37 were endodontically filled before surgery (Figure 1B), and then the extirpation of the tumour and the surrounding bone with nerve preservation was done. The teeth 33, 35 and 36 were extracted and the teeth 31, 32 and 37 were apiectomized (Figure 1C).

The postoperative course was uneventful with good bone regeneration (Figure 1D). A

long-term follow-up and an implant-prosthetic treatment is planned.

Discussion

The relative frequency of AF among odontogenic tumours seen at the Clinical Department of Maxillofacial and Oral Surgery in Ljubljana (1.8%) is within the frequencies described in the literature,⁵ although in some other countries it is more frequent.⁶ The age of described patient is above the mean age at presentation being 14.8 years.³ Our AF was incidentally found as 17% of the cases in a survey of 24 cases of AF from the Armed Forces Institute of Pathology.⁷

An aggressive surgical treatment is suggested by some authors because of the possibility of malignant transformation of an AF to an ameloblastic fibrosarcoma.^{8,9} Muller *et al.*⁸ reported that since 1960 44% cases of ameloblastic fibrosarcoma (19/43) arose from AF. There is also the consideration that the majority, if not all, of AFs are true neoplasms with a potential to recur and/or of malignant transformation and that some, especially those occurring during childhood, could represent the primitive stage of a developing odontoma.¹⁰

The recurrence rate of AF found by Trodahl *et al.*⁷ was 43.5%; on the other hand

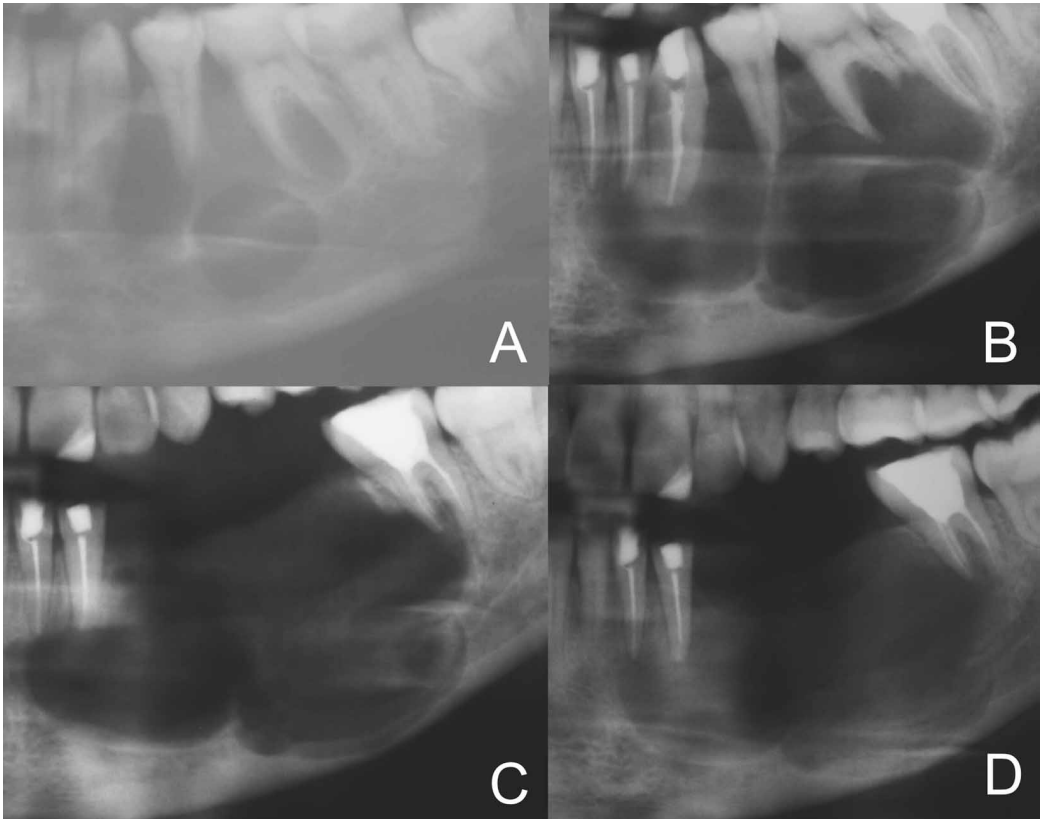


Figure 1. A - March 2004 when the lesion was discovered; B - preoperative dental panoramic tomogram (July 2005); C - postoperative dental panoramic tomogram; D - two months after the operation.

by Zallen *et al.*¹¹ it was 18.3% after reviewing the literature with 85 cases of AF. Lysell and Sund¹² proposed the incomplete primary removal as a reason of recurrence in their cases. This was supported by Mosby *et al.*¹³ explaining that after the complete removal of a tumour clinically, this cannot be stated at a cellular level. They suggest the conservative removal of AF and modified block resection of any recurrence. No matter what the reason of recurrence is, all authors agree that a long-term follow-up is necessary.

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case report

Erlotinib in previously treated non-small-cell lung cancer

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Background. Erlotinib is a novel biological anti-tumour agent in the treatment of advanced non small cell lung cancer. It represents the molecularly-targeted therapy which has been studied extensively.

Case report. We present a case of a patient who suffered from advanced non-small-cell lung cancer. After the progress of disease following a prior chemotherapy he was treated with erlotinib with remarkable effect which was shown at chest x ray and symptoms were quite reduced.

Conclusions. In selected patients with advanced non-small-cell lung cancer Erlotinib improves survival and symptom control as it results in presented case.

Key words: carcinoma, non-small-cell lung; antineoplastic agents

Introduction

In Europe lung cancer ranks first among all cancers and cancer related deaths in men and fourth in women. Similarly in Slovenia lung cancer ranks first in men with 787 new cases in year 2002 and fifth in women with 258 cases.¹ Between 80 - 85% of cases are non small cell lung cancers. A majority of patients is presented in advanced or locally advanced stages, and therefore these patients are not candidates for potentially curative resection. In patients with advanced disease our current treatment of choice is platinum based

chemotherapy with the newer agents, mostly with gemcitabine in the initial setting.^{2,3} For patients who progress after achieving response to the primary treatment therapeutic option is the treatment with taxanes (e.g.docetaxel),⁴ pemetrexed⁵ or a novel antitumour agent in a clinical trial.⁶⁻⁸

Over the past few years, a number of new agents have become available for the treatment of metastatic non-small-cell lung cancer, including the inhibitors of receptors of tyrosine kinase.^{9,10} Such a novel biological antitumor agent is erlotinib (Tarceva).^{11,12} Erlotinib is a small molecule inhibitor of HER1/EGFR tyrosine kinase; chemically it belongs to the quinazoline class and is orally available.¹³ It binds to an intracellular part of epidermal growth factor receptor and decreases tumour proliferation, invasion, metastases formation angiogenesis and tumour cell adhesion, while it increases apoptosis and probably also the sensitivity to

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Figure 1. Lung tumour after chemotherapy; visible nonhomogenous lung infiltrates



Figure 2. Lung tumour two month after therapy with erlotinib; lung infiltrates in regression

chemotherapy. Among patients with non-small-cell lung cancer who receive erlotinib, the presence of an EGFR mutation may increase responsiveness to the agent, but it is not indicative of a survival benefit.^{14,15}

In 2005 we enrolled in the study treatment with erlotinib through Tarceva EAP (extended access protocol). In this report we would like to present a case of our first patient treated with erlotinib.

Case report

Fifty-eight-year old male patient was presented for the first time in year 2003. He suffered from fatigue and dyspnoea on exercise. These symptoms lasted for two years.

The patient was a former smoker who smoked for 30 years up to 20 cigarettes a day; seven years ago he stopped smoking.

On chest X ray there was a left sided pleural effusion and indurated right hilus.

Bronchoscopy revealed stenosis of the middle lobe bronchus and bronchus for the 6th left lobe, where mucosa was also granulated and bled at touch.

Histologically invasive adenocarcinoma was confirmed in specimen taken at bronchoscopy. Cytology of pleural effusion was twice negative at malignant cells.

At the clinical examination we found a lymph node at the right supraclavicular region.

The initial stage at diagnosis was T4N3Mx; re-evaluation of native chest X rays showed metastatic lesions in both lungs, therefore the stage was T4N3M1.

The patient was in good condition, Karnofsky performance status at the time of diagnosis was assessed at 80%.

The patient received chemotherapy with cisplatin and gemcitabine in the prolonged infuse for 6 cycles, the maximal response was stagnation. The leading symptom was dyspnoea.

Ten months after the completion of treatment chest X ray showed a progressing in lung, while the performance status deteriorated gradually.

In February 2005 the patient started the treatment with erlotinib. At the beginning of the treatment chest x ray showed the left sided pleural effusion, with patchy infiltrates centrally in both lungs, while in the periphery there were multiple small nodular lesions (Figure 1).

After a month of the treatment with erlotinib the patient's general condition improved and his breathing improved too. Of the adverse effects he presented with GII rash.

The improvement was seen also in chest X ray, with diminishing and rarefication of nodes shown in the periphery and also with the improvement of centrally located infiltrate.

After two months of the treatment there was a further regression of all lesions seen on X ray (Figure 2).

The patient resumed with his work as a public employee.

Until January 2006 the patient was in a partial remission. He was employed; his only complaint was rash, which persisted.

Upon progression the patient had more infiltrates on X ray, his performance status was still excellent (Karnofsky 90).

The patient continued treatment with chemotherapy with paclitaxel and carboplatinum.

Discussion

In advanced non small cell lung cancer the aim of the treatment is to improve the survival and the quality of life (ref. meta-analysis).³

The survival in advanced non small cell lung cancer is still not as good as in some other types of advanced cancer (e. g. breast).^{16,17} The treatment with platinum based doublets had achieved some degree of the disease control but the survival remains in range of 9 months to 1 year.^{16,18} This has been improved slightly by the introduction of the second line chemotherapy with docetaxel or pemetrexed, which have a moderate efficacy and is reasonably well tolerated.^{4,5,8}

However, the mode of action of erlotinib differs from that of less specific agents - both, in terms of anti-tumour activity and side effects.¹⁹ The use of erlotinib is not connected with any significant degree of nausea and vomiting, the main side effect remains rash, which is usually well manageable and does not interfere with everyday functioning.²¹

Care should be taken of diarrhoea, which can be potentially life threatening so it is vital to ensure the patient's compliance with regimen and understanding of specific side effects.²² Oral medication is usually preferred over i. v. infusion. But one must bear in mind that specific targeting of erlotinib means also that a significant proportion of patients receiving the drug will not benefit from it and that those would therefore benefit from early discontinuation and change of the treatment strategy.

We can, therefore, presume that in selected patients, erlotinib not only improves the survival, but also improves the quality of life.^{8,15} According to the study by Sheppard *et al.*, this beneficial effect is not restricted only to female Asian non-smokers with lung adenocarcinoma but also to other patients as our patient witness.⁶

However, a careful monitoring of patient is needed and a discontinuation of the treatment at first signs of progressive disease and the reconsideration of other treatment options is warranted.

Our patient was not chemo-naïve, but received only the first line chemotherapy, so there is still a chance that he will respond to the second line chemotherapy. Furthermore, as his performance status improved, he is now probably a better candidate for the further treatment.

Conclusions

The patient we are presenting has clearly benefited from the treatment with erlotinib. However, even though he has progressed after a year of the treatment he is still in a better clinical condition as before the treatment, likewise, despite his progression, radiologically his tumour burden is still smaller than before the treatment.

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Phytohaemagglutinin as a modulator of DNA repair measured by chromosome aberration analysis in micronucleus assay in ionizing radiation biodosimetry

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Background. There are some correlations between cell's ability to remove DNA damage and proliferative activity. The aim of this study was to examine the influence of phytohaemagglutinin (PHA) on DNA repair capacity in isolated human lymphocytes exposed to ionizing radiation.

Methods. Lymphocytes were isolated from the whole blood using a Ficoll centrifugation. As the source of γ -rays ^{60}Co source Alcon, CGR-MeV was used. To achieve the absorbed dose of 2 Gy a total exposure to radiation lasted for 1.24 minutes at room temperature. Possible differences in DNA repair efficiency were monitored by chromosomal aberration analysis and micronucleus assay, 48 and 72 h after the PHA stimulation, respectively.

Results. The number of dicentric chromosomes and acentric fragments were significantly increased in lymphocytes stimulated by phytohaemagglutinin immediately after the irradiation compared to the cultures where the activator was added after 1, 2 and 4 h. The micronucleus assay did not show any significant differences in the number and distribution of micronuclei regardless of the time when the mitogen activator was added.

Conclusions. The observed non-significant decreases in the total number of chromosomal aberration and micronuclei suggest that phytohaemagglutinin does not significantly contribute to the DNA repair.

Key words: ionizing radiation; DNA damage; DNA repair; phytohaemagglutinins; chromosome aberrations; micronucleus test

Introduction

During the last few decades ionizing radiation became unavoidably present in human lives. It is widely used in the variety of medical diagnostic procedures as electric energy source of nuclear power plants. It affects a human organism on daily basis in the form of cosmic radiation. Since air flights are becoming more common way of travelling, and it is

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known that cosmic radiation is significantly higher in upper layers of the atmospheres, the total dose population is expected to increase. It is known that ionizing radiation (IR) deposits its energy in cellular structures through discrete ionization events that are essentially randomly distributed in space. Unlike chemical agents, whose damaging potential is strongly dependent on diffusion processes and thus may be affected by sub-cellular structures, IR is highly penetrating: the physics and subsequent chemistry associated with the photon absorption and the ionizing events that occur along fast electron track are complete within a few microseconds.¹ Ionizing radiation causes a wide spectrum of chemically different types of lesions in DNA of which the so-called locally multiply damaged sites (LMDS) are assumed to be biologically most important.^{2,3} LMDS may consist of single-strand breaks (SSB) on opposite strands that, if located close to each other, may give rise to double strand breaks (DSB).⁴ Thus, DSB induced by IR may arise as a direct consequence of one or more ionizing events or indirectly as a base or sugar damage on opposite strands. Ionizing radiation in physicochemical interaction with cellular DNA also produces a variety of primary lesions, alkali-labile sites, DNA-DNA and DNA-protein crosslinks, and damage to purine and pyrimidine bases.⁵⁻⁸ DNA double strand breaks (DSB) are the most serious form of DNA damage. There are two pathways for the repair of DSB.⁹ One is homologous recombination (HR) which occurs during late S and G2 phase of the cell cycle and the other pathway is non homologous DNA end joining (NHEJ). It is predominant during G0, G1 and S phase of the cell cycle.¹⁰ If not repaired, DNA lesions could cause cell death. If misrepaired, DSBs contribute to chromosomal aberrations and genomic instability. Ionizing radiation produces chromosome aberrations (involving two chromatids) at the S phase and the chromatid aberrations at G2.

To detect genetic alterations at the chromosome level using chromosome aberration and micronucleus assay the cells should be induced to enter the G1 phase and undergo division.¹¹⁻¹⁴

Phytohaemagglutinin (PHA) selectively stimulates T lymphocytes to enter mitosis. The widespread popularity of peripheral blood culture as means of chromosome analysis has been largely dependent on that mitogen.¹⁵⁻²³ There is some correlation between cell's ability to remove the DNA damage and its proliferative activity. It is well established that unstable aberrations like dicentric chromosomes, chromosome breaks and acentric fragments can be eliminated during the cell division. It was suggested that the regulation of DNA repair is dependent on cell cycle. It involves the expression of DNA repair enzymes within the defined program of gene control during the cell cycle. Some authors have shown that immediately after the irradiation mitogen-stimulated cells have a higher frequency of chromosome aberrations than the cells resting in G₀ phase before the addition of mitogens.¹⁵

Our study aimed to examine the influence of PHA on DNA repair capacity of isolated human lymphocytes. Cell cultures were started and PHA was added 0, 1, 2 and 4 h after the irradiation. Possible differences in the DNA repair efficiency was monitored by chromosomal aberration analysis and micronucleus assay, 48 and 72 h after the PHA stimulation, respectively.

Methods

Isolation of lymphocytes

The whole blood sample was taken from the cubital vein of a healthy adult male volunteer using heparinized vacutainer (Becton Dickinson, USA). There is no record that prior to the study the volunteer was exposed to any physical or chemical agent that might in-

terfere with the results. Lymphocytes were isolated from the whole blood sample by a Ficoll centrifugation method.²⁴ One milliliter of the whole blood was resuspended in 8 ml of Ham's F-10 essential medium supplemented with L-glutamine, bovine serum (20%), penicillin (100 I.U./ml) and streptomycin (100 µg/ml).

Irradiation of isolated lymphocyte

As the source of γ -rays ⁶⁰Co source Alcyon, CGR-MeV was used. Vacutainer containing isolated lymphocytes was mounted in an acrylic phantom (dimensions: 20x20x15 cm³), in depth of 5.5 cm, transversally to the axis of the irradiation. The radiation field was 15 x 15 cm², and the distance between the surface of phantom and the source of radiation was 80 cm. At total exposure to radiation lasted for 1.24 min at room temperature, thus the absorbed dose was 2 Gy.

Cultivation of lymphocytes

Phytohaemagglutinin (Murex Biotech Ltd.) (0,2ml) was added to lymphocyte cultures either immediately after the irradiation or after a certain recovery period (1, 2 or 4 h). Meanwhile cultures were held at 37°C.¹³ Since the analysis was done in duplicate, for each stimulation time, 4 different cultures were started: for the chromosomal aberration analysis and for the micronucleus assay.

The analysis of structural chromosome aberrations

The structural chromosome aberration analysis test was performed according to current IAEA guidelines.²⁵ Simultaneously with cultures for the micronuclei assay, cultures for the chromosome aberration test were set up in the same manner. Duplicate cultures per sample were set up and incubated at 37°C for 48 h. After the PHA stimulation to arrest dividing lymphocytes in metaphase, colchicine

(Sigma) (0.004%) was added 2 h prior to the harvest. Cultures were centrifuged at 1000 rpm for 10 min, the supernatant was carefully removed, and the cells were resuspended in a hypotonic solution (0.075M KCl) at 37°C for 20 min. After the second centrifugation, the cells were fixed with a freshly prepared fixative of ice-cold methanol/glacial acetic acid (v/v 3:1). Fixation and centrifugation were repeated several times until the supernatants were clear. The cell suspension was dropped onto microscope slides and left to air-dry. Slides were stained with 5% Giemsa solution (Merck). For each stimulation analysis was done in duplicate, a total number of 200 metaphases was scored. Structural chromosome aberrations were classified based on the number of sister chromatids and breakage events involved. Only metaphases containing 46 centromeres were analyzed. A total number of each type of aberrations, as well as the percentage of aberrant cells per subject were evaluated.

Micronucleus assay

The micronucleus assay was performed as described by Fenech and Morley with some modifications.²⁶ After the irradiation lymphocyte cultures were set up by adding 1 ml of isolated lymphocytes to 8 ml of F-10 medium (Sigma) supplemented with foetal calf serum (Sigma) and antibiotics penicillin (Pliva) and streptomycin (Krka). Following the stimulation with PHA, lymphocytes were incubated in vitro for 72 h at 37°C. Cytochalasin-B (Sigma) at the final concentration of 6 mg/ml was added to each culture at 44 h, and the cells were harvested after a further incubation of 28 h. After the treatment with physiological saline, cells were fixed with cold fixative, a mixture of methanol: acetic acid (v/v 3:1). The fixation step was repeated twice and cells were resuspended in a small volume of fixative solution and dropped onto clean slides.

Finally, they were stained with 5% aqueous solution of Giemsa dye (Merck) for 10 minutes. For each stimulation the analysis was done in duplicate, thus a total of 500 binuclear lymphocytes were scored. The data are expressed as the number of micronuclei per 500 binucleated cells as well as the frequency of binucleated cells containing one or more micronuclei.

Statistical analysis

The statistical significance of the results obtained was evaluated using the χ^2 - test. The level of statistical significance was set at 5%. Chi-Square test was used to compare the frequencies of chromosomal aberration and micronuclei.

Results

Chromosomal aberration analysis

The number of dicentric chromosomes and acentric fragments was found to be significantly increased in all irradiated lymphocytes regardless of the start point of the PHA stimulation compared to the control ($p < 5\%$). In irradiation exposed sample there were 97 acentric fragments and 12 dicentrics observed in

PHA stimulated lymphocytes whereas in the control no dicentrics and 4 acentric fragments were found. The number of aberrations between cultures stimulated 1, 2 and 4 hours after the irradiation did not differ significantly ($p < 5\%$).

In cultures stimulated with PHA 1, 2 and 4 hours after the irradiation the number of acentric chromosomes and dicentric chromosomes significantly decreased compared to the cultures where mitogen was added immediately after the irradiation. One hour after the irradiation the number of acentrics was 57, two hours after the irradiation the number of acentric chromosomes was 69 and four hours after the irradiation the number of acentrics was 48. The number of dicentric chromosomes decreased compared to the number of acentric chromosomes. Immediately after the irradiation the number of dicentric chromosomes was 12, one hour after the stimulation the number of dicentrics was 1. Still, the difference in the number of dicentrics was not found to be significant (Table 1).

Micronucleus assay

Using micronucleus assay no significant differences in number of micronuclei were ob-

Table 1. Total number and distribution of chromosome aberrations in isolated human lymphocytes stimulated to proliferate after the indicated post-irradiation periods. Two hundred cells were analyzed per each PHA stimulation point.

Time after irradiation	Total number of aberrations	Chromatid breaks	Chromosome breaks	Acentric fragments	Dicentric chromosomes	%of cells with aberrations
Isolated lymphocytes irradiated with 2 Gy						
0 h	112 ^a	3	/	97 ^a	12 ^a	38.0
1 h	58 ^{a,b}	/	/	57 ^{a,b}	1	21.5
2 h	76 ^{a,b}	1	1	69 ^{a,b}	5	29.0
4 h	53 ^{a,b}	/	/	48 ^b	5	23.0
Non-irradiated samples						
Lymphocytes	4	/	/	4	/	2.0
Whole blood	2	/	/	2	/	1.0

^astatistically significant compared to the control $P < 0.05$

^bstatistically significant compared to the 0h PHA stimulation point $P < 0.05$

Table 2. Frequencies of micronuclei in binucleated human lymphocytes stimulated to proliferate after the indicated post-irradiation periods. Five hundred cells were analyzed per each PHA stimulation point.

Time after irradiation	Cells without MN	Cells with MN	S MN / 500 cells	Distribution of micronuclei				MN / Cell
				1 MN	2 MN	3 MN	4 MN	
Isolated lymphocytes irradiated with 2 Gy								
0 h	396	104	116	94	8	2	/	0.23
1 h	411	89	104	74	15	/	/	0.21
2 h	399	101	117	89	9	2	1	0.23
4 h	411	89	95	83	6	/	/	0.19
Non-irradiated samples								
Lymphocytes	499	1	1	1	/	/	/	0.002
Whole blood	498	2	3	1	1	/	/	0.006

MN = micronuclei

served, regardless of the time mitogen activator was added. In irradiated cultures the number of micronuclei per cell ranged from 0.19-1.23 compared to the control where it was 0.002.

Discussion

This study presented the possible influence of phytohaemagglutinin on DNA-repair scoring the number of chromosome aberrations and micronuclei. To initiate DNA damage lymphocytes were irradiated with 2 Gy^{22,23} using a γ -ray ^{60}Co source. The number of acentric fragments was significantly increased in lymphocytes stimulated by phytohaemagglutinin immediately after the irradiation compared to the cultures where the activator after 1, 2 and 4 h was added (Table 1). That finding could indicate that DSB repair mechanisms are efficient in G_0 phase of the cycle and/or that the stimulation of lymphocytes to undergo division without having time to eliminate the majority of the DNA lesions in G_0 phase increases a misrepair rate resulting in the increased number of chromosome type aberrations. These results support the finding that the formation of unstable aberrations is cell cycle dependent and that most of double strand breaks can be fixed in first 24 h after the irradiation.²⁷

The same result but with different approach was observed by Mayer *et al.* They showed that a higher level of the DNA repair events in stimulated cells does not necessarily reflect a higher DNA repair capacity. Additionally, they showed that all repair proteins needed for the repair of γ -irradiation induced DNA-damage are already present in G_0 cells at sufficient amounts and do not need to be induced once lymphocytes are stimulated to start cycling.²⁸ Only specific DNA repair genes were found to be up-regulated after the PHA stimulation of which most have an additional function in the DNA replication. The mitogen stimulation of lymphocytes may result in an increased removal of only specific types of DNA lesions as it was reported by other authors.^{29,30} This observation might be explained by the cell cycle dependent regulation of specific DNA repair enzymes, that are more active in proliferating than in resting cells or by differences in the availability of deoxyribonucleotides which are necessary for the DNA excision repair which is not involved in DSB repair.^{30,31} Mayer *et al.*²⁸ identified only 12 genes that responded with a more than 2-fold increase of transcripts to the mitogenic stimulus, with a maximum induction for each of the genes 72 h after the PHA treatment. A decrease in the number of chromosome type aberrations with the delay of PHA stimuli could indicate the gradual activation of addi-

tional repair capacities, but still the decrease was not found to be significant. That observation is in the correlation with findings that more than 70% of all evaluated genes had constant expression levels within a twofold range compared to unstimulated.²⁸

As shown in the Table 2. no significant differences were observed in the number of micronuclei, regardless of the time point when the mitogen activator was added. Nevertheless, the number of micronuclei for specific PHA stimulation point was significantly higher than the number of chromosomal type of aberrations. It indicates that all micronuclei formed do not originate from acentrics only but also from entire chromosomes.³² Microtubules remain unsorted within the mitotic plane forming micronuclei.¹¹ Obtained results could indicate that the repair of those lesions is not dependent on the time passed between the irradiation and the mitogen stimulation. Our results show the baseline level of frequency of micronuclei after 3 cell cycles which is the same as Ramirez *et al.* observed.³² The observed non-significant decreases in the total number of chromosomal aberration and micronuclei suggest that phytohaemagglutinin does not significantly contribute to the DNA repair. We could say that in order to maximize the sensitivity of the chromosomal aberration analysis phytohaemagglutinin has to be added immediately after the irradiation.

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review

The role of p38 MAP kinase in cancer cell apoptosis

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Background. Cellular behaviour in response to many extracellular stimuli is mediated through MAP kinase signalling pathways. p38 MAP kinase that is represented in mammals by four isoforms (p38 α , p38 β , p38 γ and p38 δ) is one of the four main subgroups of MAP kinases. Recent studies show that p38 activation is necessary for cancer cell death initiated by variety of anti-cancer agents. This finding connected cancer therapies previously considered to be mechanistically unrelated and raised the possibility of developing anti-cancer agents that lack the side effects caused by events upstream of p38 MAPK. Many of the details of p38 induced apoptosis still need to be elucidated. Since most of the past studies rely only on the cell culture models, all the results have to be verified using in vivo models. Also very little is known about the role of p38 mediated apoptosis on non-neoplastic cells in response to anti-cancer agents.

Conclusion. Although p38 activation of cancer cell apoptosis is a very complex process, recent studies indicate a good starting point for new strategies that would increase the efficiency and decrease the toxicity of proven therapies.

Key words: tumor cells, cultured; apoptosis; MAP kinase; antineoplastic agents

Introduction

Many extracellular stimuli are converted into specific cellular responses through the activation of mitogen-activated protein kinase (MAPK) signalling pathways. MAPKs are serine/threonine protein kinases that can phosphorylate both cytoplasmic and nuclear targets.^{1,2} Four distinct subgroups within the

MAP kinase superfamily have been described: extracellular signal-regulated kinases (ERKs), c-jun N-terminal or stress-activated protein kinases (JNK/SAPK), ERK/big MAP kinase 1 (BMK1), and the p38 group of protein kinases.³ The p38 group is in mammals represented by four isoforms (p38 α , p38 β , p38 γ and p38 δ) with overlapping but also distinct physiological roles.⁴ Among them, p38 α is the best characterized isoform. Recently, it was observed that retinoids, cisplatin and also other chemotherapeutic agents initiate cancer cell apoptosis through the activation of p38 MAP kinase. This finding connects cancer therapies previously considered to be mechanistically unrelated and raises the possibility of developing anti-cancer agents that

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lack the side effects caused by events upstream of p38 MAPK.⁵ The potential therapeutic value of p38 and the availability of specific chemical inhibitors made these protein kinases the subject of intensive studies during the past years.¹

The focus of this review will be to highlight the characteristics and components of the p38 pathway, its role in cancer cell apoptosis and to indicate possible implications for cancer therapy.

The p38 MAP kinase signalling pathway

p38 MAP cascade regulates a variety of cellular responses to environmental stress, pro-inflammatory cytokines, lipopolysaccharide (LPS) and other signals and was first described in 1994.⁶⁻⁸ The cascade consists of three conserved kinase modules that include MAPK kinase, which activates MAPK kinase that in turn activates MAPK, in our case p38 (Figure 1). p38 MAPK responds to the signal by becoming rapidly activated by dual phosphorylation of the Thr-Gly-Tyr (TGY) motif.⁹ Four isoforms of the p38 family have been identified in mammals: p38 α (p38),⁶⁻⁸ p38 β ,¹⁰ p38 γ ¹¹ and p38 δ ,¹² which differ in their tissue expression and affinity for upstream activators and downstream effectors.⁴ Among them, p38 α and p38 β show a relatively broad tissue expression in contrast to p38 γ and p38 δ that are differentially expressed depending on the tissue type.¹³ A major contribution to the studies of p38 α and p38 β isoforms is the availability of specific inhibitors, developed principally using 2,4,5-triaryl imidazoles as a template.¹⁴

There are two main MAPKKs that are known to activate p38, MKK3¹⁵ and MKK6.¹⁶ While MKK6 is a common activator of all p38 isoforms, MKK3 is unable to activate p38 β despite 80% homology between these two MKKs. In specific cell types also MKK4, an upstream kinase of JNK, can aid in the activation of

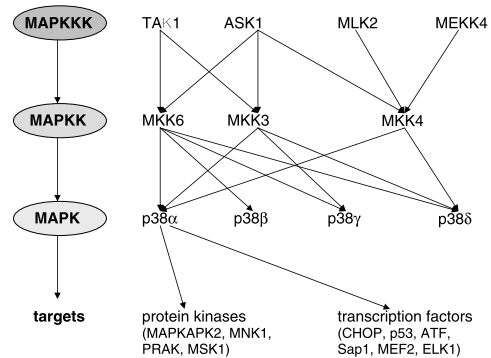


Figure 1. p38 MAP kinase signalling pathway (according to reference 3).

p38 α and p38 δ . In addition to activation with upstream kinases there is also a MAPKK-independent mechanism of p38 activation involving TAB1, with no known biological context.³

The diverse range of MAPKKKs, upstream activators of MKKs, is responsible for susceptibility of p38 to such a wide range of extracellular stimuli. This MAP3K includes TAK1,¹⁷ ASK1¹⁸ DLK/MUK/ZPK, MLK2 and MEKK4.¹⁹ The upstream of MAPKKs are also low molecular weight GTP-binding proteins from the Rho family and p21- activated kinases.³

The MAP kinase activation is often transient under physiological conditions, being downregulated by dephosphorylation of various members of the MAP kinase pathway. The proteins responsible for that are different dual-specificity phosphatases, all grouped in the MAP kinase phosphatase (MKP) family.²⁰

Activated p38 MAP kinase regulates the activity of a wide range of protein kinases (MAPKAPK2, MNK1, PRAK, MSK1), transcription factors (CHOP, p53, ATF-1/2/6, Sap1, MEF2, ELK1 and others) and some other proteins, which then further regulate the activity of their targets. This complicated network of interacting proteins is in consequence responsible for different cell activities, like apoptosis, cell-cycle arrest, cytokine production, cell differentiation, cell senescence and tumour suppression.^{3,5}

The role of p38 in apoptosis in cancer cells

Apoptosis is an active form of cell death that plays an essential role in eliminating damaged cells or cells with defects in key-regulated processes such as growth.²¹ Once this highly regulated process is triggered, the apoptotic program involves activation of a series of biochemical events that end with the release of proteins from the mitochondria into the cytoplasm and the nucleus.²² Not surprisingly, several tumours emerge with mutations in genes conferring apoptosis resistance, allowing them to continue uncontrolled growth under, for normal cells, pro-apoptotic conditions.²³

There are some evidence for pro-apoptotic and anti-apoptotic role of p38 MAPKs, depending on the cell type and the stimuli. Overexpression of the active form of the p38 activator MKK6 protects cardiac myocytes from β -adrenergic receptor-mediated apoptosis.²⁴ Similarly, the early activation of p38 is necessary and sufficient to protect Kym cells from tumour necrosis factor- α -mediated apoptosis,²⁵ and expression of p38 β results in attenuated cell death induced by Fas ligand and UV light²⁶. The activation of p38 may also protect through the down-regulation of the Fas receptor expression.²⁷

Even more reports support the pro-apoptotic role of p38, for example, p38 is a mediator of apoptosis in neurons²⁸ and cardiac cells.²⁹ In other cell types, p38 activates apoptosis upon stimulation with tumour necrosis factor- α ³⁰, transforming growth factor- β ³¹ or in response to oxidative stress.³² The latter was also demonstrated in the case of TRAIL induced apoptosis mediated by reactive oxygen species (ROS)-activated p38 MAP kinase followed by the caspase activation in HeLa cells.³³ Cells treated with betulinic acid, a selective inhibitor of human melanoma, also induce apoptosis through the ROS mediated p38 activation.³⁴

The mechanisms by which p38 contributes to an enhanced pro-apoptotic response in-

clude the phosphorylation and translocation of proteins from the Bcl-2 family, which leads to the release of cytochrome c from the mitochondria,^{32, 35} the transforming growth factor- β -induced activation of caspase 8³⁶ as well as the regulation of membrane blebbing and nuclear condensation.³⁷ At the transcriptional level, expression of monoamine oxidase²⁸ or growth arrest and DNA damage (GADD)-inducible genes³⁸ have been shown to mediate pro-apoptotic effects of p38. The importance of p38 in apoptosis was also shown in the study of apoptotic response in different p38-deficient cells, like primary fibroblasts and immortalized cardiomyocytes and fibroblasts. All p38 deficient cells were more resistant to apoptosis induced by many different stimuli. The reduced apoptosis correlated with down-regulation of the proapoptotic proteins Fas and Bax as well as enhanced activity of the ERK survival pathway.³⁹

This opposing effects on apoptosis observed for p38 probably reflect the multiple and complex activities of this signalling pathway, which acts on different targets at once and thus can yield distinct overall effects depending on the cellular context. Similar opposing effects were also found for the other stress-activated protein kinase JNK.³⁷

p38, a convergence point in cancer therapy?

Recent studies show that the p38 MAP kinase activation is necessary for cancer cell death initiated by various anti-cancer agents. Retinoids like 13-*cis* retinoic acid or all-*trans* retinoic acid (ATRA) initiate apoptosis in medulloblastoma cell lines by phosphorylating p38 MAPK through the induction of bone morphogenetic protein 2 (BMP2).⁴⁰ Another synthetic retinoid CD437 induces apoptosis in ovarian carcinoma cell culture also in p38 dependent way. The activated p38 phosphorylates the transcription factor MEF-2, which has a proposed role in mitochondrial depolar-

ization and apoptosis. In these cells ATRA does not induce p38 cascade, suggesting a distinct upstream mechanism from the one described for medulloblastoma.⁴¹

Four chemotherapeutic agents were shown to induce the p38 activation and mitotic cell-cycle arrest in HeLa human cervical carcinoma cells by depolymerizing microtubules, (nocodazole, vincristine and vinblastine) or stabilizing them (taxol). The extent of apoptosis in these cells is greater when induced by a direct activation of p38, because previously mentioned chemotherapeutics activate pro-apoptotic as well as pro-survival pathways in HeLa cells, which results in less apoptosis. The activated p38 induces cell death by stimulating translocation of Bax from the cytosol to the mitochondria. On the other hand, the p21-activated kinase (PAK) mediates cell survival by phosphorylating Bad, thereby inhibiting its pro-apoptotic function.⁴²

The activation of p38 in several tumour cell lines was also observed after the treatment with cisplatin, an inorganic heavy metal coordination complex, and doxorubicin, a DNA intercalating agent.⁴³

Some anti-cancer agents utilize two distinctive MAPK signalling pathways for killing cells. Phytosphingosine simultaneously downregulates the ERK survival pathway, which is critical for the death receptor independent activation of caspase-8, and activates p38 pathway, which is involved in the cell death pathway through the mitochondrial activation.³⁵ Another example is 2-methoxyestradiol (2-ME) apoptosis induction in prostate cancer cell line. A treatment with 2-ME leads to the p38 activation as well as JNK-mediated Bcl2 phosphorylation, which inactivates this anti-apoptotic protein.⁴⁴

All these reports support the role of p38 MAPK as the key component for the cancer cell death after treating tumours with a variety of anti-cancer agents. This finding connects cancer therapies previously considered to be mechanistically unrelated and raises the

possibility of developing anti-cancer agents with the lack of the side effects caused by events upstream of p38 MAPK.⁵

Still many of the details of p38 induced apoptosis need to be elucidated. Since most of the past studies rely only on the cell culture models, all the results have to be verified using in vivo models. Also very little is known about the role of p38 mediated apoptosis on non-neoplastic cells in response to anti-cancer agents. The issue is also the drug resistance, therefore, more has to be learned about how tumours protect themselves from the pro-apoptotic activation of p38 MAPK. The study made on 20 liver cancer specimens shows that both MKK6 and p38 protein levels are lower in hepatocellular carcinoma tumours than adjacent non-neoplastic liver. This reduction of p38 levels could represent an anti-apoptotic mechanism that provides growth advantage to tumour cells.⁴⁵

Conclusions

Although the p38 activation of cancer cell apoptosis is a very complex process, recent studies indicate a good starting point for new strategies that would increase the efficiency and decrease the toxicity of proven therapies. One possible way to improve the efficiency would be by treating patients simultaneously with available p38-activating agents and antagonists of anti-apoptotic pathways, like PAK and ERK inhibitors. An alternative strategy would be to use combinations of p38-activating chemotherapeutics.

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Radiol Oncol 2005; 40(1): 1-5.

Majhna količina proste plevralne tekočine. Drugi del - fiziološka plevralna tekočina

Kocijancič I

Izhodišča. V literaturi je le nekaj člankov, ki poročajo o možnostih rentgenskega in ultrazvočnega prikaza fiziološke plevralne tekočine pri zdravih. V zadnjem desetletju je napredek ultrazvočne tehnologije omogočil prikaz majhnih količin fiziološke plevralne tekočine pri približno 20 % zdrave populacije. Ob določenih fizioloških stanjih, kot je na primer nosečnost, je prikaz fiziološke plevralne tekočine z ultrazvokom bolj pogost.

Zaključki. Pomembno je, da pozitivnega izvida brez spremljajočih kliničnih sprememb ne ocenimo za znak bolezni.

Radiol Oncol 2006; 40(1): 7-15.

Ocena Parksovega kota pri bolnikih z motnjami odvajanja blata - prospektivna raziskava z defekografijo

Kołodziejczak M, Sudoł-Szopińska I, Grochowicz M, Bochenek A, Świątłowska M

Izhodišča. Defekografijo uporablja veliko kolorektalnih kirurgov, ker lahko z njo anatomsko in dinamično proučujejo odvajanje blata. S preiskavo ugotovimo anorektalno funkcijo in delovanje medeničnega dna ter anatomske nepravilnosti.

Metode. V prospektivni raziskavi smo z defekografijo proučili 58 bolnikov (50 žensk in 6 moških), ki so bili stari od 24 do 83 let (povprečno 58,3 leta) in so imeli proktološke težave. Bolniki so opisovali nezmožnost zadrževati blato, občutek obstrukcije v rektumu, zaprtost, zdrs rektuma in rektalno razjedo. Velikost Parksovega kota smo merili pred odvajanjem blata, med napenjanjem in med odvajanjem blata. Merili smo tudi trajanje sfinkterske relaksacije, trajanje odvajanja blata in gibljivost medenične prepone.

Rezultati. Nenormalne vrednosti Parksovega kota smo ugotavljali pred odvajanjem blata in med napenjanjem pri bolnikih, ki niso uspeli zadrževati blato, ki so imeli občutek obstrukcije v rektumu ali so bili zaprti. Pri zdrsu rektuma pa omenjene nenormalne vrednosti nismo zasledili. Defekografija nam je pomagala odkriti rektokelo pri bolnikih, ki so tožili zaradi zaprtosti in občutka obstrukcije v rektumu. Koristna je bila tudi pri oceni bolnikov, ki so imeli rektalno razjedo.

Parksov kot se je med odvajanja blata spreminjal, trajanje sfinkterske relaksacije pa je bilo spremljivo ne glede na vrsto bolezni.

Zaključki. Defekografija je koristna metoda pri motorični oceni odvajanja blata pred in po kirurškem zdravljenju.

Radiol Oncol 2006; 40(1): 57-62.

Lhermitte-Duclosova bolezen in nosečnost

Franko A, Holjar-Erloč I, Miletić D, Petrović O

Izhodišča. Lhermitte-Duclosova bolezen ali displastični gangliocitom malih možganov je redka bolezen, ki lahko povzroča napredujočo tumorsko rast. Ugotovimo jo z magnetno resonanco, ki pokaže značilne neobarvane girusne spremembe, različne intenzitete na T1 In T2 magnetnih slikah.

Prikaz primera. Opisujemo 37-letno bolnico, ki smo ji dokazali Lhermitte-Duclosovo bolezen v tretjem tromesečju nosečnosti.

Zaključki. Prikazan primer kaže, da lahko nosečnica z Lhermitte-Duclosovo boleznijo brez življenjskega tveganja donosi in rodi zdravega otroka. Potrebni pa je več izkušenj, da bi to opažanje lahko posplošili.

5-letno preživetje ter pogostnost lokalne in regionalne ponovitve bolezni pri bolnicah z rakom dojke, ki smo jih zdravili z ohranitveno operacijo in obsevanjem

Rajer M, Majdič E

Izhodišča. Ohranitveno zdravljenje je del standardne terapije bolnic z začetnim rakom dojke. V naši raziskavi smo skušali ugotoviti, kakšno je 5-letno preživetje, pogostnost lokalne in regionalne ponovitve bolezni ter ugotoviti morebitne dejavnike tveganja, ki na to vplivajo.

Metode. Od januarja 1998 do decembra 1999 smo na Onkološkem inštitutu v Ljubljani zdravili 564 bolnic z rakom dojke v prvem in drugem stadiju bolezni. Pri vseh smo določili naslednje dejavnike: starost, histološko diagnozo, stopnjo malignosti, velikost tumorja, število metastatskih pazdušnih bezgavk, prisotnost hormonskih receptorjev, ekstenzivno intraduktalno komponento, vaskularno invazijo, stanje resekcijskih robov, vrsto operacije in način dopolnilnega zdravljenja.

Rezultati. Povprečna starost bolnic je bila 54,2 let. Najpogostejša histološka diagnoza je bila invazivni duktalni karcinom. Največ tumorjev je bilo druge stopnje malignosti. Večina tumorjev je bila T1 (72%), sledijo tumorji T2 (24%). Metastaze v pazdušnih bezgavkah je imelo 44% bolnic. Vse so bile zdravljene z ohranitveno operacijo in pooperativnim obsevanjem operirane dojke. Polovica bolnic je dobila dopolnilno kemoterapijo in hormonsko terapijo. Celokupno petletno preživetje je bilo 88,5%. Statistično značilni napovedni dejavniki so bili: velikost tumorja, število metastatskih pazdušnih bezgavk, stopnja malignosti, prisotnost hormonskih receptorjev in vaskularna invazija. Starost bolnic in histološki tip tumorja nista vplivala na preživetje. Lokalno ponovitev bolezni smo ugotovili pri 4,3% bolnic, regionalno pri 3,4%. Od 19 regionalnih ponovitev bolezni je bil ena v pazduhi, ena parasternalno in ostale v supraklavikularni loži.

Zaključki. Ugotovili smo, da sta celokupno 5-letno preživetje ter pogostnost lokalne in regionalne ponovitve bolezni pri naših bolnicah primerljivi z rezultati v drugih raziskavah. Stopnja malignosti, hormonski status in število pozitivnih bezgavk so napovedni dejavniki, ki napovedujejo tako celokupno preživetje kot lokoregionalno ponovitev bolezni, medtem ko se v naši raziskavi starost bolnic ni pokazala kot napovedni dejavnik.

Radiol Oncol 2006; 40(1): 29-33.

Zmanjšana moč vratnih iztegovalnih mišic (sindrom padajoče glave) kot posledica obsevalnega zdravljenja

Bhatia S, Miller RC, Lachance DL

Izhodišča. Sindrom padajoče glave je redka bolezen, pri kateri bolnik ne more držati glave vzravnano v anatomske legi. Nastane zaradi zmanjšanja moči vratnih iztegovalnih mišic.

Prikaz primera. Prikazujemo primer sindroma padajoče glave pri bolnici, ki je bila pred deseti leti obsevana zaradi Hodgkinovega limfoma, predhodno pa se je zdravila tudi zaradi multiple skleroze. Razpravljamo o možnih vzrokih nastanka bolezni.

Zaključki. Najbolj verjeten vzrok nastanka bolezni je bila poškodba prednjega roga hrbtenjače ob obsevanju, kar je povzročilo poškodbo spodnjega motoričnega nevrona in mišično atrofijo.

Radiol Oncol 2005; 40(1): 35-8.

Ameloblastični fibrom

Božič M, Ihan Hren N

Izhodišča. Ameloblastični fibrom je redek odontogeni tumor. Sestavljen je iz odontogenega ekto- mezenhima podobnega dentalni papili ter epitelija podobnega dentalni lamini in sklenini, je brez trdih zobnih tkiv.

Prikaz primera. Opisujemo bolnico z velikim ameloblastičnim fibromom, ki se je razraščal v spodnji čeljustnici in je segal od spodnjega levega drugega sekalca (32) do spodnjega levega drugega kočnika (37). Po do sedaj zbranih podatkih je to prvi opisani primer ameloblastičnega fibroma v Sloveniji.

Zaključki. Zaradi možnosti ponovitve bolezni pa tudi spremembe ameloblastičnega fibroma v ameloblastični sarkom svetujemo radikalno kirurško zdravljenje in daljše pooperativno sledenje bolnikov.

Radiol Oncol 2006; 40(1): 57-62.

Radiol Oncol 2006; 40(1): 39-42.

Erlotinib pri zdravljenju nedrobnoceličnega raka pljuč

Smrdel U, Kovač V

Izhodišča. Erlotinib je novo biološko protitumorsko zdravilo, ki ga uporabljamo pri bolnikih z nedrobnoceličnim rakom pljuč. Predstavlja molekularno tarčno terapijo, ki so jo zelo intenzivno proučevali v kliničnih študijah.

Prikaz primera. Predstavljamo bolnika, ki smo ga obravnavali zaradi razširjene oblike nedrobnoceličnega raka pljuč. S kemoterapijo smo dosegli stagnacijo bolezni, ki je po desetih mesecih ponovno napredovala. Splošno stanje se je izrazito poslabšalo. Že po enem mesecu ponovnega sistemskega zdravljenja, tokrat z erlotinibom, so simptomi izzveneli in na rentgenski sliki prsnih organov vidimo znatno zmanjšanje bolezenskih sprememb (delno remisijo).

Zaključki. Pri izbranih bolnikih z nedrobnoceličnim rakom pljuč lahko erlotinib podaljša preživetje in znatno zmanjša simptome bolezni.

Radiol Oncol 2006; 40(1): 43-9.

Fitohemaglutinin kot modulator DNK popravljalnih mehanizmov merjenih s številom kromosomskih aberacij in z mikronukleus testom po obsevanju z ionizirajočim sevanjem

Đurinec M, Želježić D in Garaj-Vrhovac V

Izhodišča. Obstaja korelacija med sposobnostjo popravila poškodb DNK in sposobnostjo delitve celic. Zato je bil namen študije ugotoviti vpliv fitohemaglutinina (PHA) na sposobnost popravila DNK poškodb pri izoliranih humanih limfocitih, obsevanih z ionizirajočim sevanjem.

Metode. Limfociti so bili izolirani na Fikol gradientu. Za obsevanje celic smo uporabili ⁶⁰Co izvor proizvajalca Alcon. Celice so bile obsevane 1,24 minut pri sobni temperaturi, tako smo dosegli absorbirano dozo 2 Gy. Razlike v sposobnosti popravila DNA poškodb smo merili s številom kromosomskih aberacij in z mikronukleus testom 48 in 72 ur po PHA stimulaciji.

Rezultati. Število dicentričnih in acentričnih kromosomov je bilo signifikantno povečano pri celicah, ki so bile stimulirane s PHA takoj po obsevanju, ne pa pri celicah, kjer smo dodali PHA 1, 2 ali 4 ur kasneje. Mikronukleus test ni pokazal signifikantnih razlik v distribuciji ne glede na čas dodanega fitohemaglutinina.

Zaključek. Rezultati nakazujejo, da fitohemaglutinin ne vpliva signifikantno na popravljalne mehanizme DNK.

Radiol Oncol 2006; 40(1): 57-62.

Vloga p38 MAP kinaze pri apoptozi rakavih celic

Lenassi M, Plemenitaš A

Izhodišča. Odzivanje celic na številne zunajcelične signale poteka preko aktivacije MAP kinaznih signalnih poti. Ena od štirih glavnih podskupin MAP kinaz je p38 MAP kinaza, ki je pri sesalcih prisotna v štirih izooblikah: p38 α , p38 β , p38 γ in p38 δ . Nedavne raziskave so pokazale, da je za aktivacijo apoptoze rakavih celic z različnimi kemoterapevtiki nujna aktivacija p38 kinaze. To spoznanje je v eni točki povežalo poti delovanja raznolikih kemoterapevtikov ter s tem nakazalo nove možnosti njihovega razvoja brez stranskih učinkov, ki jih sedaj povzročajo dogodki pred aktivacijo p38. Veliko podrobnosti o p38 posredovani apoptozi je potrebno še razjasniti. Dosedanja dognanja je potrebno preveriti v in *vivo* modelih, saj se ta sedaj nanašajo predvsem na celične kulture. Malo je znanega tudi o vlogi p38 pri apoptozi nerakavih celic po aktivaciji s kemoterapevtiki.

Zaključki. Čeprav je p38 posredovana aktivacija apoptoze rakavih celic zelo kompleksen proces, novejša študije ponujajo dober začetek za razvoj novih kemoterapevtikov s povečano učinkovitostjo in zmanjšano toksičnostjo.

Notices

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

Lung cancer

April 19-26, 2006

The "2nd Latin American Conference on Lung Cancer" will be offered in Cancun, Mexico.

Contact E-mail: LungCancerLA@meet-ics.com; or see [http:// www.LCLA2006.com](http://www.LCLA2006.com)

Molecular oncology

April 30 - May 4, 2006

The ESTRO teaching course "Molecular Oncology for the Radiation Oncologist" will take place in Granada, Spain.

Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Radiotherapy

May 7-11, 2006

The ESTRO teaching course "Dose Determination in Radiotherapy: Beam Characterisation, Dose Calculation and Dose Verification" will take place in Izmir, Turkey.

Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Radiology

May 15-17, 2006

The UK radiological congress will be held in Birmingham, UK.

Contact UKRC 2006 Organisers, PO Box 2895, London W1A 5RS, UK; or call + 44(0) 207 307 1410/20; or fax +44(0) 207 307 1414; or e mail conference@ukrc.org.uk / exhibition@ukrc.org.uk; or see [http:// www.ukrc.org.uk](http://www.ukrc.org.uk)

Bioethics

May 18-20, 2006

The ESO advanced course "Ethics in Oncology" will take place in Bled, Slovenia.

Contact Ms. Rita De Martini, European School of Oncology, Via del Bollo, 4, 20123 Milan, Italy; or call +39 02 85 46 45 27; or fax +39 02 85 46 45 45; or e-mail rdemartini@esoncology.org; or see <http://www.cancerworld.org/eso>

Oncology

June 2-5, 2006

The 6th international cell death symposium on "The Mechanisms of Cell Death" will take place in Angra dos Reis, Brazil.

Contact International Cell Death Society, Victoria Matassov, Secretary, c/o Queens College, CUNY 65-30 Kissena Blvd. Flushing, NY 11367-1575; or call +1 718 997 3450; or fax +1 718 997 3429; or e-mail vmatasso@qc1.qc.edu; or see <http://www.celldeath-apoptosis.org>

Clinical oncology

June 2-6, 2006

The 42nd ASCO Meeting will be offered in Atlanta, USA.

Contact E mail: enews@asco.org; or see <http://www.asco.org>

Radiotherapy

June 11-15, 2006

The ESTRO teaching course "Imaging for Target Volume Determination in Radiotherapy" will take place in Athens, Greece.

Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Cancer research

June 17-23, 2006

The 8th intensive workshop for European junior clinical oncologists "Methods in Clinical Cancer Research" will take place in Flims, Switzerland.

Contact Federation of European Cancer Societies (FECS), Avenue E. Mounier, 83, B-1200 Brussels, Belgium; or call +32 2 775 02 06; or fax +32 2 775 02 45; or e-mail workshop@fecsc.be; or see <http://www.fecsc.be>

Lung cancer

June 18-21, 2006

The "10th Central European Lung Cancer Conference" will be offered in Prague, Czech Republic.

Contact: +420-608-408-708; or e-mail celcc@conference.cz; or see <http://www.conference.cz/celcc2006>

Prostate cancer

June 25-27, 2006

The ESTRO teaching course "Brachytherapy for Prostate Cancer" will take place in Barcelona, Spain.

Contact ESTRO office, Avenue E. Mounierlaan 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Bronchology

June 25-28, 2006

The 14th Word Congress of Bronchology and the 14th Word Congress of Bronchoesophagology will take place in Buenos Aires, Republic Argentina.

Contact: General Secretariat, Ms. María Graziani & Asociados with phone +4394 7726 4393 3437; or Fax: +541 439 33436; or E-mail: mg@mariagraziani.com

Radiotherapy

June 25-29, 2006

The ESTRO teaching course "IMRT and Other Conformal Techniques in Practice" will take place in Copenhagen, Denmark.

Contact ESTRO office, Avenue E. Mounierlaan 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Radiol Oncol 2006; 40(1): 63-6.

Clinical trial statistics

June 28-30, 2006

The EORTC (European Organisation for Research and Treatment of Cancer) course "Clinical Trial Statistics for Non Statisticians" will take place in Brussels, Belgium.

Contact Danielle Zimmermann, EORTC Education Office, Avenue E. Mounier 83 B. 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 62 33; or e-mail dzi@eortc.be; or see <http://www.eortc.be>

Lung cancer

June 30 - July 2, 2006

Inaugural IASLC Australian Lung Cancer Conference on Multidisciplinary Care will be offered in Palm Cove, North Queensland, Australia.

Contact E-mail fongk@health.qld.gov.au

Cancer research

July 1-4, 2006

The "19th Meeting of the European Association for Cancer Research EACR 19" will take place in Budapest, Hungary.

Contact EACR-19 Secretariat, Federation of European Cancer Societies, Avenue E. Mounier, 83, B-1200 Brussels, Belgium; or call +32 2 775 02 01; or fax +32 2 775 02 00; or e-mail EACR19@fecsc.be; or see <http://www.fecsc.be>

Gynaecological malignancies

August 31 - September 1, 2006

The ESTRO teaching course "Brachytherapy for Gynaecological malignancies" will take place in Vienna, Austria.

Contact ESTRO office, Avenue E. Mounierlaan 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Radiotherapy

September 3-7, 2006

The ESTRO teaching course "Physics for Clinical Radiotherapy" will take place in Innsbruck, Austria.

Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Oncology

September 8, 2006

The EORTC (European Organisation for Research and Treatment of Cancer) course "One-Day Introduction to EORTC Trials" will take place in Brussels, Belgium.

Contact Danielle Zimmermann, EORTC Education Office, Avenue E. Mounier 83 B 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 62 33; or e-mail dzi@eortc.be; or see <http://www.eortc.be>

Radiobiology

September 17-21, 2006

The ESTRO teaching course "Basic Clinical Radiobiology" will take place in Lisbon, Portugal.

Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Lung cancer

September 25-26, 2006

The "2nd International Workshop Early Invasive Lung Cancer: New Diagnostic Tools & Treatment Strategies" will be held in Turin, Italy.

Contact E-mail: a.crippa@congressiefiere.com or see <http://www.congressiefiere.com>

Otorhinolaryngology

September 27-30, 2006

The 11th Danube Symposium 2006 "International Otorhinolaryngological Congress" will take place in Bled, Slovenia.

Contact Albatros Bled, Ribenska 2, 4260 Bled, Slovenia; or call +386 4 5780 350; or fax +386 4 5780 355; or e-mail info@albatros-bled.com; or see <http://www.albatros-bled.com>

Oncology

October 8-12, 2006

The ESTRO 25 / ECCO 14 Conference will take place in Leipzig, Germany.

Contact FECS office, Av. E. Mounierlaan, 83/4, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estroweb.org>

Radiation oncology

October 22-27, 2006

The ESTRO teaching course "Evidence-Based Radiation Oncology: Methodological Basis and Clinical Application" will take place in Giardini Naxos, Italy.

Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Lung and head & neck

October 26-28, 2006

The "4th Lung & Head and Neck Conference" will be offered in Chicago, Illinois.

Contact: Taryn Klocke; call +1 770-984-5113; or e-mail evokes@medicine.bsd.uchicago.edu

Oncology

October 26-29, 2006

The "2nd Congress of the Polish Oncology" will take place in Poznan, Poland.

See <http://www.kongresonkologii.pl>

Lung cancer

November 8-12, 2006

The "3rd IASLC/ASCO/ESMO International Conference on Targeted Therapies in Lung Cancer" will be held in Taormina, Sicily, Italy.

Contact E-mail: fred.hirsch@UCHSC.edu

Head & neck

November 16-18, 2006

The "5th European Workshop on Basic Biology of Head & Neck Cancer" will take place in Poznan, Poland.

See <http://www.ori.amp.wdu.pl/5workshop>

Radiotherapy

November 19-23, 2006

The ESTRO teaching course "IMRT and Other Conformal Techniques in Practice" will take place in Gliwice, Poland.

Contact ESTRO office, Avenue E. Mounierlaan 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Surgical oncology

November 30 - December 2, 2006

The "13th Congress of the European Society of Surgical Oncology ESO 2006" will take place in Venice, Italy.

Contact Conference Secretariat, ESO 2006, Federation of European Cancer Societies, Avenue E. Mounier, 83, B-1200 Brussels, Belgium; or call +32 2 775 02 01; or fax +32 2 775 02 00; or e-mail ES-2006@fecs.be; or see <http://www.fecs.be>

Radiotherapy

December 3-7, 2006

The ESTRO teaching course "Image-guided Radiotherapy (IGRT)" will take place in Brussels, Belgium.

Contact ESTRO office, Avenue E. Mounierlaan 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see <http://www.estro.be>

Toxicology

July 15-19, 2007

The "11th International Congress of Toxicology" will be offered in Montreal, Canada.

Contact Congress Secretariat, e-mail: ict2007@nrc-nrc.gc.ca; or see <http://www.ict2007.org>

Lung cancer

September 2-6, 2007

The "12th World Conference on Lung Cancer" will be offered in Seoul, Korea.

Contact Conference Secretariat; e-mail WCLC2007@ncc.re.kr; or see <http://www.iaslc.org/lumages/12worldconfannounce.pdf>

Oncology

September 23-27, 2007

The "14th European Cancer Conference ECCO 14" will take place in Barcelona, Spain.

Contact Conference Secretariat, ECCO 14, The European Cancer Conference, European Cancer Societies (FECS), Avenue E. Mounier, 83, B-1200 Brussels, Belgium; or call +32 2 775 02 01; or fax +32 2 775 02 00; or e-mail ECCO14@fecs.be; or see <http://www.fecs.be>

Lung cancer

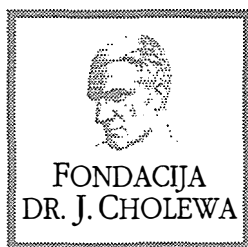
August 21-24, 2009

The "13th World Conference on Lung Cancer" will be offered in San Francisco, USA.

Contact Conference Secretariat; e-mail WCLC2007@ncc.re.kr; or see <http://www.iaslc.org/lumages/12worldconfannounce.pdf>

As a service to our readers, notices of meetings or courses will be inserted free of charge.

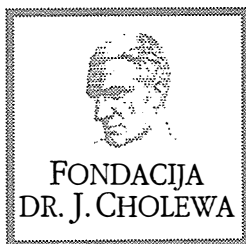
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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education - a report for the first quarter of 2006

The Dr. J. Cholewa Foundation for Cancer Research and Education is a modern and dynamic institution, trying to respond to all the contemporary challenges that fall upon it in its mission to support activities associated with cancer research and education in Slovenia. As it deals with bestowing different grants and other forms of financial support to persons interested in cancer research and education in Slovenia, all the requests are being dealt with responsibly by Foundation members with clinical and research experience in cancer and by members with important experience in finance. With this in mind, the Foundation will also continue to support the publication of the results from research it supported in respectable international scientific oncology journals and in more novel electronic forms of dissemination of scientific information.

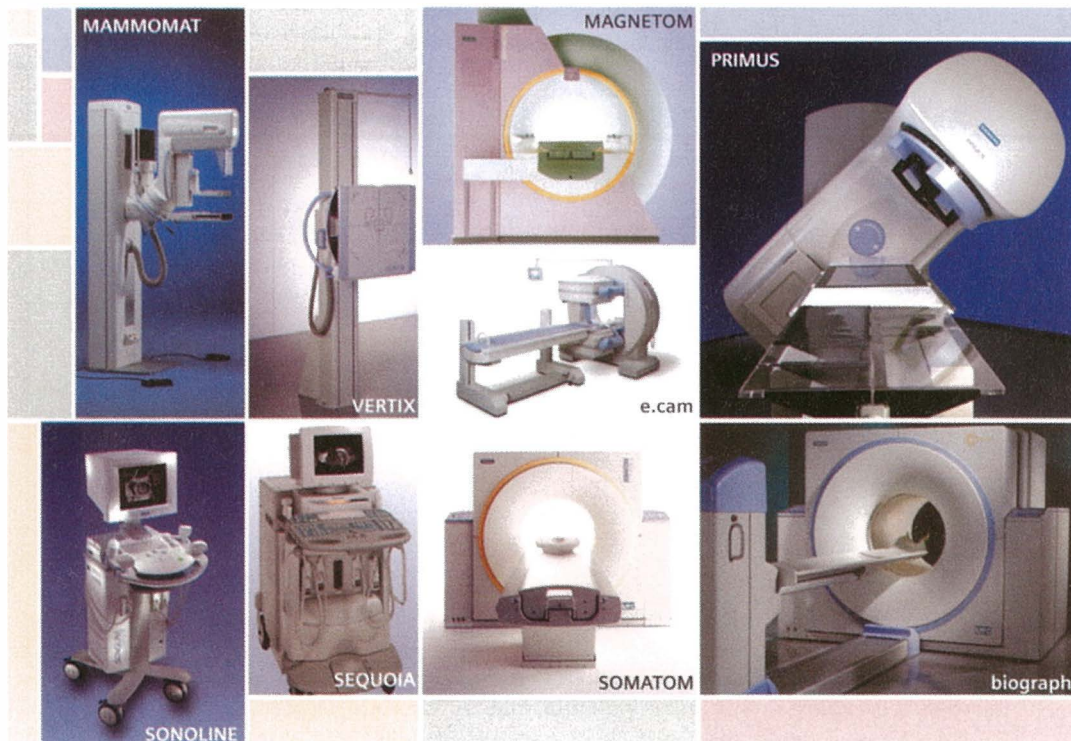
The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the regular publication of "Radiology and Oncology" international scientific journal, which is edited, published and printed in Ljubljana, Slovenia, as it has done over the last couple of years. This support is considered to be one of its more important commitments. The Foundation also remains active in promoting cancer education in general, especially in general population, and among younger scientists with a particular interest in cancer research. It is worth mentioning that many study and research grants have been already bestowed to young researchers from various scientific fields associated with oncology in Slovenia and that many of them were also given grants to attend scientific meetings, conferences and symposia dealing with oncology worldwide. The information and knowledge of cancer in general and problems associated with cancer research have thus spread as a result of these activities and the Dr. J. Cholewa Foundation for Cancer Research and Education has a special reason to respectfully acknowledge the importance of the commitment of various public companies and private individuals to its cause.

It is the policy of the Dr. J. Cholewa Foundation for Cancer Research and Education to lend support to individuals and institutions that participate in cancer research and education Slovenia with the idea that cancer research should be further encouraged in all parts of the country where the interest for such research exists.

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



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- Visoko specifično monoklonsko IgG1 protitelo, ki kompetitivno inhibira receptorje za epidermalni rastni faktor (EGFR)
- Učinkovitost je dokazana v kombinaciji z irinotekanom¹



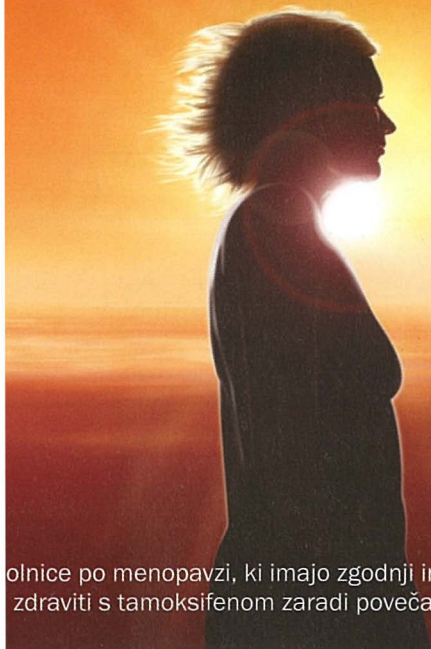
Merck v onkologiji | biološko zdravljenje za boljšo kakovost življenja

Erbix 2 mg/ml raztopina za infundiranje (skrajšana navodila za uporabo)

Cetuximab je himeno monoklonsko IgG1 protitelo, ki je usmerjeno proti receptorju za epidermalni rastni faktor (EGFR). **Terapevtske indikacije:** Zdravilo Erbitux je v kombinirani terapiji z irinotekanom indicirano za zdravljenje bolnikov z metastatskim rakom debelega črevesa in danke z ekspresijo receptorjev za epidermalni rastni faktor (EGFR), in sicer po neuspešni citotoksični terapiji, ki je vključevala tudi irinotekan. **Odmerjanje in način uporabe:** Zdravilo Erbitux infundirajte enkrat na teden z intravensko infuzijo prek linijskega filtra. Začetni odmerek je 400 mg/m² telesne površine. Naslednji tedenski odmerki so vsak po 250 mg/m². Priporočljivo je, da z zdravljenjem s cetuximabom nadaljujete do napredovanja osnovne bolezni. **Kontraindikacije:** Zdravilo Erbitux je kontraindicirano pri bolnikih z znano hudo preobčutljivostno reakcijo (3. ali 4. stopnje) na cetuximab. **Posebna opozorila in previdnostni ukrepi:** Pojav hude preobčutljivostne reakcije (3. ali 4. stopnje) zahteva takojšnjo in stalno ukinitve terapije s cetuximabom. **Neželeni učinki:** Pri približno 5% bolnikov se lahko pojavijo preobčutljivostne reakcije. Približno polovica teh reakcij je hudih. Pri približno 5% bolnikov lahko pričakujemo konjunktivitis. O dispneji so poročali pri 25% bolnikov z rakom debelega črevesa in danke v zadnjem stadiju. Hude kožne reakcije se pojavijo v približno 15%, predvsem nastopijo v obliki aknam podobnega izpuščaja in/ali motenji nohtov. Če se pri bolniku pojavi huda kožna reakcija (stopnje 3), smete zdravljenje nadaljevati le, če se je reakcija pomirila do 2. stopnje. **Pakiranje:** 1 viala po 50 ml. Vsak ml raztopine vsebuje 2 mg cetuximaba.

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

¹) Cunningham D et al., Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer, New ENG J Med 2004; 351(4): 337-345



bolnice po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji in se ne morejo zdraviti s tamoksifonom zaradi povečanega tveganja za tromboembolizem ali nenormalnosti endometrija.

Arimidex vodilni zaviralec aromataze

anastrozol

Kratka informacija o zdravlilu Arimidex 1 mg

stav: Filmsko obložena tableta vsebuje 1 mg anastrozola.

Indikacije: Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji in se ne morejo zdraviti s tamoksifonom zaradi povečanega tveganja za tromboembolizem ali nenormalnosti endometrija. Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana in pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.

Merjenje in način uporabe: 1 tableta po 1 mg peroralno, enkrat na dan. Pri zdravljenju raka je priporočljivo trajanje zdravljenja 5 let.

Kontraindikacije: Arimidex je kontraindiciran pri: ženskah pred menopavzo, nosečnicah in doječih materah, ženskah s hujšo ledvično odpovedjo (očistek kreatinina manj kot 20 ml/min (oziroma 3 ml/s)), bolnicah z zmernim do hudim boleznijo in bolnicah, ki imajo znake preobčutljivosti za anastrozol ali za katerekoli drugo sestavino zdravila. Zdravila, ki vsebujejo estrogen, ne smete dajati skupaj z Arimidexom, ker bi se njegovo onkološko delovanje izničilo. Tamoksifena ne smete uporabljati skupaj z Arimidexom,

ker lahko pride do zmanjšanja njegovega delovanja.

Posebna opozorila in previdnostni ukrepi: Uporabe Arimidexa ne priporočamo pri otrocih, ker njegova varnost in učinkovitost pri njih še nista raziskani. Menopavzo je potrebno biokemično določiti pri vseh bolnicah, kjer obstaja dvom o hormonskem statusu. Ni podatkov o varni uporabi Arimidexa pri bolnicah z zmerno ali hudo jetrno okvaro ali hujšo ledvično odpovedjo (očistek kreatinina manj kakor 20 ml/min (oziroma 0,33 ml/s)). Ni podatkov o uporabi anastrozola z analogi LHRH. Te kombinacije zdravil se ne sme uporabljati zunaj kliničnih preskušanj. Pri ženskah z osteoporozo ali pri ženskah s povečanim tveganjem za razvoj osteoporoze je treba določiti njihovo mineralno gostoto kosti z densitometrijo, na primer s slikanjem DEXA na začetku zdravljenja, pozneje pa v rednih intervalih. Po potrebi je treba začeti z zdravljenjem ali preprečevanjem osteoporoze in to skrbno nadzorovati. Ni verjetno, da bi Arimidex zmanjšal bolnično sposobnost za vožnjo ali upravljanje s stroji. Ker pa so med uporabo Arimidexa poročali o splošni oslabelosti in zaspanosti, je potrebna previdnost pri vožnji in upravljanju strojev, dokler simptoma trajata.

Nosečnost in dojenje: Arimidex je med nosečnostjo in dojenjem kontraindiciran.

Neželeni učinki: Najpogostejši neželeni učinki so navali vročine, suhost vagine in redčenje las. Ostali neželeni učinki vključujejo gastrointestinalne motnje (anoreksija, slabost, bruhanje, diareja), astenijo, bolečine/okorelost v sklepih, zaspanost, glavobol in izpuščaje. Občasna poročila navajajo krvavitev iz nožnice, ki se pretežno pojavlja pri bolnicah z napredovalim obolenjem raka na dojki v prvih tednih po prehodu z dotedanjega hormonskega zdravljenja na zdravljenje z Arimidexom. Če krvavitev traja dlje časa, so potrebne dodatne preiskave. Hiperholesterolemija, običajno blaga do zmerna. O povišanih nivojih gama-GT in alkalne fosfataze so poročali le občasno. Vzročna povezanost omenjenih sprememb ni bila ugotovljena.

Medsebojno delovanje z drugimi zdravili: Zdravila, ki vsebujejo estrogen, ne smete dajati sočasno z Arimidexom, ker bi se njegovo onkološko delovanje izničilo. Tamoksifena se ne sme uporabljati skupaj z Arimidexom, ker lahko pride do zmanjšanja njegovega delovanja.

Vrsta ovojnine in vsebina: Pretisni omoti iz PVC in aluminija, ki vsebujejo 28 tablet v škatlici.

Režim izdaje zdravila: Rp/Spec

Datum priprave informacije: oktober 2005
Pred predpisovanjem, prosimo, preberite celoten povzetek temeljnih značilnosti zdravila.

datne informacije in literatura so na voljo pri:

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slabosti in bruhanja**

- Preprečevanje navzeje in bruhanja, povezanih z zmerno emetogeno kemoterapijo raka¹
- Preprečevanje akutne in zapoznele navzeje in bruhanja, povezanih z zelo emetogeno terapijo raka s cisplatinom¹

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Literatura: 1. Arhiv MSD, Slovenija.

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Zdravilo se izdaja le na zdravniški recept (H/Rp).

[†] Zaščitena blagovna znamka MERCK & Co., Inc., Whitehouse Station, N. J., ZDA.

EMEND 80mg trde kapsule
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Terapevtske indikacije:

Preprečevanje akutne in zapoznele navzee in bruhanja povezanih z zelo emetogeno kemoterapijo raka s cisplatinom. Preprečevanje navzee in bruhanja, povezanih z zmerno emetogeno kemoterapijo raka.

EMEND se daje v sklopu kombiniranega zdravljenja (glejte poglavje 4.2 v Povzetku glavnih značilnosti zdravila).

Odmerjanje in način uporabe:

EMEND je na voljo v obliki 80 mg in 125 mg trdih kapsul.

EMEND se daje 3 dni po shemi zdravljenja, ki vključuje kortikosteroid in antagonist 5-HT₃. Priporočeni odmerek zdravila EMEND je 125 mg peroralno prvi dan ter 80 mg enkrat na dan drugi in tretji dan.

Podatkov o učinkovitosti pri kombiniranju z drugimi kortikosteroidi in antagonisti 5-HT₃ ni dovolj.

EMEND se lahko jemlje s hrano ali brez. Trdo kapsulo je treba pogoltniti celo.

Starejši bolniki: Pri starejših bolnikih odmerka ni treba prilagajati.

Okvara ledvic: Pri bolnikih z okvaro ledvic in pri bolnikih s končno ledvično odpovedjo, ki se zdravijo s hemodializo, odmerka ni treba prilagoditi.

Okvara jeter: Pri bolnikih z blago okvaro jeter odmerka ni treba prilagajati. Pri bolnikih z zmerno okvaro jeter so podatki omejeni, podatkov pri bolnikih s hudo okvaro jeter ni na voljo.

Otroci in mladostniki: Varnost in učinkovitost pri otrocih in mladostnikih nista znani. Uporabe pri bolnikih, ki so mlajši od 18 let, zato ne priporočamo.

Kontraindikacije: Preobčutljivost za zdravilno učinkovino ali katero koli pomožno snov.

Zdravila EMEND se ne sme uporabljati sočasno s pimizdom, terfenadinom, z astemizolom ali s cisapidom.

Posebna opozorila in previdnostni ukrepi:

Podatki o uporabi pri bolnikih z zmerno okvaro jeter so omejeni. Podatkov o uporabi pri bolnikih s hudo okvaro jeter ni na voljo. Pri teh bolnikih je treba aprepitant uporabljati previdno.

EMEND je treba uporabljati previdno pri bolnikih, ki sočasno jemljejo zdravila, ki se primarno presnavljajo s CYP3A4. Zato je treba previdno uporabljati kemoterapevte, ki se presnavljajo s CYP3A4. Še posebej je previdnost potrebna pri sočasnem dajanju irinotekana, saj lahko kombinacija poveča toksični učinek.

Pri sočasni uporabi EMEND-a z alkaloidi rženega rožička (ergot alkaloidi), ki so substrat za CYP3A4, se lahko zviša plazemska raven teh zdravil.

Sočasna uporaba EMEND-a z varfarinom zmanjša protrombinski čas, izražen kot INR (*International Normalised Ratio*). Pri bolnikih, ki se neprenehoma zdravijo z varfarinom, je treba INR skrbno spremljati med zdravljenjem z zdravilom EMEND in 2 tedna po vsakem 3-dnevnem ciklusu zdravljenja z EMEND-om.

Med jemanjem EMEND-a se lahko zmanjša učinkovitost oralnih kontraceptivov. Med zdravljenjem z EMEND-om in dva meseca po zadnjem odmerku EMEND-a je treba uporabljati alternativna ali dodatna kontracepcijska sredstva. Sočasno jemanje EMEND-a in zdravil, ki močno inducirajo aktivnost CYP3A4 (npr. rifampicin, fenitoin, karbamazepin, fenobarbital), se je treba izogibati, ker kombinacija povzroči zmanjšanje plazemskih koncentracij aprepitanta. Sočasna

uporaba EMEND-a in šentjanževke ni priporočljiva. Potrebna je previdnost pri sočasni uporabi EMEND-a in zdravil, ki zavirajo aktivnost CYP3A4 (npr. ritonavir, ketokonazol, klaritromicin, telitromicin), ker kombinacija povzroči zvišanje plazemskih koncentracij aprepitanta.

Bolniki z redkimi dednimi motnjami fruktozo intoleranco, malabsorpcijo glukoze in galaktoze ali insuficienco saharaze-izomaltaze ne smejo jemati tega zdravila.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:

Aprepitant je substrat, zmerno zaviralec in induktor CYP3A4. Aprepitant je tudi induktor CYP2C9.

Kot zmerni zaviralec CYP3A4 lahko aprepitant zviša plazemske koncentracije sočasno uporabljenih zdravil, ki se presnavljajo s CYP3A4. AUC peroralno vzetih substratov CYP3A4 se lahko poveča do približno 3-krat. Pri sočasnem jemanju s substrati CYP3A4 svetujemo previdnost.

EMEND-a se ne sme uporabljati skupaj s pimizdom, terfenadinom, z astemizolom ali s cisapidom. Aprepitant zavira CYP3A4, zaradi česar bi se lahko zvišale plazemske koncentracije teh zdravil, kar bi lahko povzročilo resne ali življenjsko ogrožajoče reakcije.

Kot zmerni induktor CYP2C9 in blag induktor CYP3A4 in glukuronidacija, lahko aprepitant zniža plazemske koncentracije substratov, ki se izločajo po teh poteh. Ta učinek se lahko pokaže šele po koncu zdravljenja z EMEND-om. Indukcija substratov CYP2C9 in CYP3A4 je prehodna, maksimalen učinek pa je dosežen v 3-5 dneh po koncu 3 dnevnega zdravljenja z zdravilom EMEND. V tem obdobju svetujemo previdnost pri dajanju peroralnih zdravil, ki se presnavljajo s CYP3A4.

Pokazano je bilo, da aprepitant inducira presnavljanje S₀ varfarina in tolbutamida, ki se presnavljata s CYP2C9. Sočasno dajanje EMEND-a in teh ali drugih zdravil, ki se presnavljajo s CYP2C9, denimo fenitoina, lahko zniža plazemske koncentracije teh zdravil, zato svetujemo previdnost.

EMEND nima medsebojnega vpliva z digoksinom, zato verjetno ne interagirata s P-glikoproteinskim prenašalcem.

Kortikosteroidi:

Deksametazon: Pri sočasnem jemanju z EMEND-om je treba običajni peroralni odmerek zmanjšati za približno 50 %.

Metilprednizolon: Pri sočasni uporabi z EMEND-om je treba običajni intravenski odmerki metilprednizolona zmanjšati za približno 25 %, običajni peroralni odmerki metilprednizolona pa za približno 50 %.

Kemoterapevte: V kliničnih raziskavah so EMEND uporabljali skupaj z naslednjimi kemoterapevti, ki se predvsem ali delno presnavljajo s CYP3A4: etopozid, vinorelbin, docetaksel in paklitaksel. Odmerkov teh zdravil niso prilagajali glede na morebitno medsebojno delovanje zdravil. Svetujemo previdnost pri bolnikih, ki dobivajo taka zdravila, je lahko potreben dodaten nadzor.

Midazolam: Pri sočasni uporabi z EMEND-om je treba upoštevati možne učinke zvišanih plazemskih koncentracij midazolama in drugih benzodiazepinov, ki se presnavljajo predvsem s CYP3A4 (alprazolam, triazolam).

EMEND poveča AUC midazolama, ki je občutljiv substrat za CYP3A4.

Varfarin: Pri bolnikih, ki se dolgotrajno zdravijo z varfarinom, je treba protrombinski čas (INR) skrbno nadzorovati med zdravljenjem z zdravilom EMEND in 2 tedna po vsakem 3-dnevnem ciklusu zdravljenja z EMEND-om.

Tolbutamid: EMEND je pri jemanju po shemi 125 mg prvi dan ter 80 mg/dan drugi in tretji dan zmanjšal AUC tolbutamida (ki je substrat za CYP2C9), ki so ga bolniki prejeli v enkratnem odmerku 500 mg per os pred začetkom 3-dnevne sheme odmerjanja EMEND-a ter 4., 8. in 15. dan, in sicer za 23 % 4. dan, za 28 % 8. dan in za 15 % 15. dan.

Oralni kontraceptivi: Med jemanjem EMEND-a se lahko zmanjša učinkovitost oralnih kontraceptivov. Med zdravljenjem z EMEND-om in dva meseca po zadnjem odmerku EMEND-a je treba uporabljati alternativne ali dodatne kontracepcijske metode.

Antagonisti 5-HT₃: V kliničnih raziskavah medsebojnega delovanja aprepitant ni imel klinično pomembnih učinkov na farmakokinetiko ondansetrona in granisetrona.

Vplivi drugih zdravil na farmakokinetiko aprepitanta

Potrebna je previdnost pri sočasni uporabi EMEND-a in zdravil, ki zavirajo aktivnost CYP3A4 (npr. ritonavir, ketokonazol, klaritromicin, telitromicin), ker se zaradi kombinacije zvišajo plazemske koncentracije aprepitanta.

Sočasno dajanje EMEND-a in zdravil, ki močno inducirajo aktivnost CYP3A4 (npr. rifampicin, fenitoin, karbamazepin, fenobarbital), se je treba izogibati, saj se pri kombiniranju zmanjšajo plazemske koncentracije aprepitanta, zaradi česar se lahko zmanjša učinkovitost EMEND-a. Sočasno uporabo EMEND-a in šentjanževke odsvetujemo.

Ketokonazol: Pri enkratnem odmerku 125 mg EMEND-a po 10-dnevne zdravljenja s ketokonazolom (ki je močan zaviralec CYP3A4) 400 mg na dan, se je AUC aprepitanta

povečal za približno 5-krat, povprečni terminalni razpolovni čas aprepitanta pa se je povečal približno za 3-krat.

Rifampicin: Pri enkratnem odmerku 375 mg EMEND-a 9 dan 14-dnevnega zdravljenja z rifampicinom (ki je močan induktor CYP3A4) 600 mg na dan, se je AUC aprepitanta zmanjšal za 91 %, povprečni terminalni razpolovni čas aprepitanta pa se je za 68 % zmanjšal.

Neželeni učinki:

Varnost aprepitanta so ocenjevali pri približno 3800 preiskovancih.

O kliničnih neželenih učinkih, ki so jih raziskovalci opredelili kot dogodke, povezane z zdravilom, so poročali pri približno 17 % bolnikov, zdravljenih z aprepitantom, ter pri 13 % bolnikov, zdravljenih z običajno terapijo (pri bolnikih, ki se zaradi raka zdravijo z zelo emetogeno kemoterapijo). Zaradi neželene učinkov so zdravljenje prekinili pri 0,6 % bolnikov, zdravljenih z aprepitantom, ter pri 0,4 % bolnikov, zdravljenih s standardno terapijo. V klinični raziskavi bolnikov, ki so dobivali zmerno emetogeno kemoterapijo, so o kliničnih neželenih učinkih poročali pri približno 21 % bolnikov, zdravljenih z aprepitantom, ter pri približno 20 % bolnikov, zdravljenih s standardno terapijo. Zdravljenje z aprepitantom so zaradi neželenih učinkov prekinili pri 1,1 % bolnikov, zdravljenih z aprepitantom, ter pri 0,5 % bolnikov, zdravljenih s standardno terapijo.

Najpogostejši neželeni učinki, o katerih so pri zdravljenju z aprepitantom pri bolnikih, ki so dobivali zelo emetogeno kemoterapijo, poročali pogostejše kot pri običajni terapiji, so bili: kolcanje (4,6 %), oslabelost/utrujenost (2,9 %), zvišanje alanin-aminotransferaze (ALT) (2,8 %), zaprtje (2,2 %), glavobol (2,2 %) ter anoreksija (2,0 %). Najpogostejši neželeni učinek, o katerem so pri bolnikih, ki so dobivali zmerno emetogeno kemoterapijo, poročali pogostejše kot pri bolnikih, ki so bili zdravljeni s standardno terapijo, je bila utrujenost (2,5 %).

Pri bolnikih, zdravljenih z aprepitantom, so opazili naslednje neželene učinke, ki so se pojavljali pogostejše kot pri običajni terapiji:

Pogoste (>1/100, <1/10): anoreksija, glavobol, omotica, kolcanje, zaprtje, driska, dispneja, erukcija, oslabelost/utrujenost, zvišanje ALT, zvišanje aspartat-aminotransferaze (AST).

Občasne (>1/1000, <1/100): kandidiza, okužbe s stafilokoki, anemija, febrilna nevropatija, pridobivanje telesne teže, polidipsija, dezorientacija, evorija, anksioznost, normalne sline, motnje mišljenja, konjunktivitis, tinitus, bradikardija, navali vročine, fangitis, kihanje, kašelj, zatekanje izcedka iz nosu v žrelo, draženje žrela, navzeja*, bruhanje*, refleks kisline, motnje okusa, neugodje v epigastriju, zaprtje, gastroezofagalna refluksna bolezen, predrtje razjede dvajsnika, bolečine v trebuhu, suha usta, enterokolitis, vetrovi, stomatitis, izpuščaji, akne, fotosenzitivnost, prekomerno potenje, mastna koža, srbenje, lezije kože, mišični krči, bolečine v mišicah, polurija, dizurija, polakisurija, bolečine v trebuhu, otekanje, zardevanje, nelagodje v prsnem košu, letargija, žeja, zvišanje alkalne fosfataze, hiperglikemija, mikrohematurija, hiponatremija, znižanje telesne teže. *Navzeja in bruhanje sta bila parametra učinkovitosti prvih 5 dni po kemoterapiji; o njih so kot o neželenih učinkih poročali šele po tem času.

Profil neželenih učinkov je bil v podaljšku raziskave z več ciklusi zdravljenja (do 5 dodatnih ciklov kemoterapije) na splošno podoben istemu po prvem ciklusu. Pri enem bolniku, ki je dobival aprepitant ob kemoterapiji zaradi raka, so poročali o Stevens-Johnsonovem sindromu kot o resnem neželenem učinku. Pri enem bolniku, ki je prejemal aprepitant, vendar ne v raziskavi CINV (Cisplatin-Induced Nausea and Vomiting), so poročali o angioedemu in kopricni kot o resnem neželenem učinku.

Aprepitanta ni mogoče odstraniti s hemodializo.

Vrsta ovojnine in vsebine: Na voljo so različna pakiranja, ki vsebujejo različne jakosti zdravila. Aluminijasti prešni omet, ki vsebuje eno 125 mg kapsulo in dve 80 mg kapsuli. Na tgu ni vseh navedenih pakiranj.

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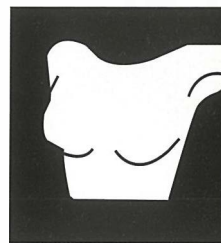
1- Tarceva (erlotinib) summary of product characteristics, F.Hoffmann-La Roche LTD., 2005.





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Announcement

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METHODOLOGY OF CLINICAL TRIALS IN ONCOLOGY

VIENNA, AUSTRIA; AUGUST 24th – 26th, 2006

- Host Institutions:** CESAR Central European Society for Anticancer Drug Research – EWIV
Applied Cancer Research – Institution for Translational Research Vienna (ACR-ITR VIENNA)
Ludwig Boltzmann-Institute for Applied Cancer Research (LBI-ACR VIENNA)
- Objective:** To provide participants with the specific knowledge on the planning and performing of clinical studies of the phase I-II-III
- Contents:** Bio-statistical issues
Preclinical data as prerequisite for the conception of clinical trials
Clinical pharmacological and toxicological issues
Planning and performing of clinical trials of the phase I-II-III
Study design for targeted therapies
Study organization/-administration
Data assessment and management
Limitations and pitfalls of clinical trials
- Course Format:** Lectures, presentation of case reports, systematic discussion and exchange of experiences among the participants and the faculty
Workshop: phase II-study protocol development
- Information:** ACR-ITR VIENNA; c/o Bernardgasse 24/2, A-1070 Vienna, Austria
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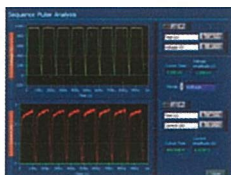
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