Malignant intraperitoneal mesothelioma-Başkent University experience

Malign intraperitoneal mezotelioma – Başkent Üniversitesi deneyimi

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Abstract

Objective: To evaluate diagnostic and treatment results of malignant intraperitoneal mesothelioma in one setting.

Materials and Method: 12 patients treated for malignant peritoneal mesothelioma from January 2007 to June 2009 in Başkent University Ankara Hospital, Department of Gynaecology and Obstetrics were evaluated. In a retrospective observational study design tumour stage, grade, differentiation, time from first symptoms, pleural involvement, peritoneal cancer index, surgical cytoreduction, chemotherapeutic regimen, number of cycles, disease free survival and overall survival were evaluated. Disease free survival, overall survival, time until first symptoms were researched.

Results: The main presenting symptom was abdominal distension. Primary cytoreductive surgery followed by chemotherapy was performed in 9 patients. In 6 patients completeness of cytoreductive score below 2 was achieved. As a first line chemotherapy the most often used was cisplatin in combination with pemetrexed. Themean time from first symptoms until the diagnosis was 1.9 months. Disease free survival of 4.4±1.0 months after completing particular treatment and overall 1-year survival of 85.7 % was observed. No correlations between first symptoms (0.27, p=0.52), time until the diagnosis (-0.29, p=0.44) and overall survival were observed. Similarly, correlations between peritoneal cancer index (0.25, p=0.67), prior surgical score (-.45, p=0.37), completeness of cytoreduction score (0.61, p=0.27) and overall survival were not observed.

Conclusions: Because of the low number of patients and different treatment approaches data from a particular patient setting are inconclusive, but from the literature there is evidence that patients with malignant intraperitoneal mesothelioma should undergo optimal cytoreduction and receive a combination of cisplatin and pemetrexed as a first line chemotherapy for intravenous or cisplatin in different chemotherapy regimens using the intraperitoneal administration route, if accessible, with even higher overall survival rates.

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Özet

Amaç: Tek bir merkezde malign intraperitoneal mezoteliomanın tanı ve tedavi sonuçlarını değerlendirmek.

Gereç ve Yöntemler: Başkent Üniversitesi Ankara Hastanesi, Kadın Hastalıkları ve Doğum Departmanında Ocak 2007 - Haziran 2009 arasında malign peritoneal mezotelioma için tedavi edilmiş 12 hasta çalışmaya alındı. Retrospektif gözlemsel çalışma dizaynında tümör evresi, derecesi, farklılaşması, ilk semptomlardan beri geçen süre, plevral tutulum, peritoneal kanser indeksi, cerrahi hücre azaltımı, kemoterapötik rejim, tedavi döngülerinin sayısı, hastalıksız sağkalım ve toplam sağkalım değerlendirildi. Hastalıksız sağkalım, toplam sağkalım, ilk semptomlara kadar geçen süre araştırıldı.

Bulgular: Başlıca başvuru semptomu karında şişkinlikti. Kemoterapinin izlediği birincil sitoredüktif cerrahi 9 hastada gerçekleştirildi. 6 hastada 2'nin altında sitoredüktif tamlığı skoruna ulaşıldı. İlk seçenek kemoterapi olarak en sık kullanılan pemetreksed ile kombinasyonda sisplatin idi. İlk semptomlardan tanıya kadar geçen ortalama süre 1.9 aydı. Belirli tedavinin tamamlanmasından sonra hastalıksız sağkalım 4.4±1.0 ay ve toplam 1-yıllık sağkalım %85.7 olarak gözlendi. Toplam sağ kalım ile ilk semptomlar (0.27, p=0.52) ve tanıya kadar geçen süre (-0.29, p=0.44) arasında korelasyon gözlenmedi. Benzer şekilde, toplam sağ kalım ile peritoneal kanser indeksi (0.25, p=0.67), önceki cerrahi skoru (-.45, p=0.37), sitoredüksiyon tamlığı skoru (0.61, p=0.27) arasında korelasyon gözlenmedi.

Sonuçlar: Düşük hasta sayısı ve farklı tedavi yaklaşımları nedeniyle bu özel hasta grubundan gelen veriler bir sonuca ulaşmamıştır, fakat literatürde malign intraperitoneal mezoteliomalı hastaların optimal sitoredüksiyon geçirmesi ve ilk seçenek kemoterapi olarak intravenöz sisplatin ve pemetreksed alması veya eğer mümkünse, daha yüksek toplam sağ kalım oranları ile, intraperitoneal uygulama yolunu kullanan farklı kemoterapi rejimlerinde sisplatin alması gerektiğine dair kanıtlar bulunmaktadır

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Introduction

Primary malignant peritoneal mesothelioma is a rare tumour with a poor prognosis. Mesotheliomas are strongly associated to asbestos exposure, but only 50% of patients having peritoneal mesotheliomas have been exposed to asbestos (1, 2). In some parts of Europe, the processing of asbestos reached its peak in the middle of the 1980s, therefore a rising number of cases is expected until 2020. The highest incidence of mesotheliomas is observed in Australia, The Netherlands, United Kingdom and Italy, varying from 33-22 cases per million (3). The overall prevalence is 1-2 cases per million. Mostly the tumour arises from mesothelial cells in the pleura, while primary malignant mesotheliomas in the abdominal cavity comprise between 10 to 40% (4-8).

Regardless of the site of origin, the prognosis is usually poor, with a median survival of 4-12 months for pleural tumours and less than 1 year for peritoneal tumours (9, 10). Successful treatment is based on early diagnosis and appropriate treatment which embraces optimal tumour debulking procedure, especially from surfaces of the parietal peritoneum, and chemotherapy. It is thought that completeness on the cytoreduction score is one of the most important prognostic factors for the treatment of malignant peritoneal mesothelioma. The overall response rate reported with a single agent chemotherapy, combined chemotherapy, intraperitoneal chemotherapy, continuous hyperthermic peritoneal perfusion are 13.1%, 20.5%, 47.4%, and 84.6%, respectively (11). Cisplatin is the most studied agent, with activity in 25% of patients (12).

The present paper reports 12 cases of malignant primary peritoneal mesothelioma who were treated by debulking surgery and systemic chemotherapy in one institution.

Material and Methods

The electronic data base at the Baskent University Hospital from January 2005 to June 2009 was reviewed retrospectively for malignant peritoneal mesothelioma and included in this study. All consecutive patients with intraperitoneal mesothelioma were included in the study. Only cases with a definitive diagnosis of peritoneal malignant mesothelioma were included. Cases were accepted as mesothelioma if the light microscopy, imunohistochemistry, and clinical/surgical findings were fully consistent with the diagnosis. Benign mesothelial lesions, such as adenomatoid tumour, well-differentiated papillary mesothelioma, localized fibrous tumours, and multicystic mesothelioma were not included the study. The staging system for malignant peritoneal mesotheliomas proposed by Sebbag and Sugarbaker was selected and in most cases tumour differentiation was reported as belonging to one of three-adonomucious, epithelial and biphasic or sarcomatous type (13). Cases with uncertain diagnosis and indistinct imunohistochemistry profile were re-evaluated by a pathologist. Finally, a total of 12 peritoneal malignant mesothelioma cases were found to be eligible to enter the study. For tumour spread and completeness of cytoreductive surgery, patients were divided as having peritoneal cancer index (PCI) above or below 28 and completeness of cytoreduction (CC) denoted with a single score from 0 to 3. The completeness of cytoreduction score is defined as follows: score “0” indicates that no visible peritoneal carcinomatosis remains after cytoreduction; score “1” indicates that tumour nodules persisting after cytoreduction are less than 2.5 mm; score “2” indicates tumour nodules between 2.5 mm and 2.5 cm and score “3” indicates tumour nodules greater than 2.5 cm or a confluence of unresected tumour nodules at any site within the abdomen or pelvis.

Presence or absence of disease involving the pleural cavity was determined by computer tomography. Thickened pleura above 10 mm or pleural effusion cytologicaly approved for malignancy were considered as having concomitant pleural disease. Overall survival (OS) was considered as a primary endpoint of the study, as secondary endpoints were disease free survival (DFS) and time from first symptoms. In some cases, it was impossible to assess disease free survival, because patients were followed up in other institutions and departments in Turkey.

Prior surgery score was assessed as a complete count of surgeries for a particular patient and evaluated for correlations with survival parameters.

All of the patients included in the analysis received only systemic chemotherapy.

For data collection and calculations SPSS 17.0 was used. Correlation analysis between patients with peritoneal cancer index above and below 28, cytoreductive score, disease free, overall survival and surgical procedures was analyzed with the nonparametric Spearman’s correlation test. For correct nonparametric correlation analysis, overall survival of patients was ranged according to those who survived more and less than one year, similarly ranging was performed for correct application of disease free survival-patients were divided in those who had disease free survival more or less than 5 months. Correlation among time from first symptoms, time to diagnosis and overall survival was assessed with parametrical Pearson’s correlation test. Statistically significant difference was accepted at level of 0.05.

Results

The age range for the patients was 26-69 years with a mean age of 57 years.

Abdominal distension was the first and most often observed symptom when patients presented to hospital or outpatient unit. Mean time from first symptoms until the diagnosis was 1.9±0.6 months with a range from 0-4.5 months. No correlations between first symptoms (0.27, p=0.52), time until the diagnosis (-0.29, p=0.44) and overall survival were observed.

Histologically, the majority of mesotheliomas were epitheloid (tubulopapillary) (10/12) with only one patient having mesothelioma of mixed subtype and one patient with biphasic subtype.

For completeness of optimal tumour debulking, such procedures as colostomy and splenectomy were performed for several patients. Parietal stripping of the peritoneum was carried out on only one patient (Table 1). There was no correlation observed between survival parameters and splenectomies (0.17, p=0.72). Correlation for colostomies was not possible to assess because

Table 1. Characteristics of serum biomarker levels, tumor dissemination, management and survival for patients included in the study

Patient number	Age	Ca-125, U/ml	PCI	CC	Surgery	Histology	Pleural disease	First line Chemotherapy	DFS, months	Alive or Dead	OS, months
1	60	106.0	> 28	1	Hysterectomy+BSO+ BPPLND+Omentectomy	Epitheloid	Yes	Cisplatin+ Pemetrexed	4.0	Dead	13.5
2	54	398.0	> 28	2	Hysterectomy+BSO+ BPPLND+Omentectomy+ Appendectomy	Epitheloid	Yes	Cisplatin+ Pemetrexed	7.0	Alive	23.0
3	67	696.2	> 28	2	Hysterectomy+BSO+ BPPLND+Omentectomy+ Appendectomy	Epitheloid	No	Cisplatin+ Gemcitabine	0.0	Dead	3.0
4	26	40.2	< 28	1	BPPLND+Omentectomy*	NA	NA	Cisplatin+ Gemcitabine	7.0	Alive	13.5
5	54	55.0	> 28	2	Hysterectomy+BSO+ BPPLND+Omentectomy+ Appendectomy+Splenectomy	Epitheloid	Yes	NA	NA	NA	NA
6	59	NA	NA		Hysterectomy+BSO+ BPPLND+Omentectomy	Mixed	Yes	Carboplatin+ Paclitaxel	7.0	Dead	60.0
7	64	35.6	> 28	2	Hysterectomy+BSO+ Omentectomy+Appendectomy	Epitheloid	Yes	NA	NA	NA	NA
8	66	24.0	> 28	2	Hysterectomy+BSO+ BPPLND+Omentectomy+ Appendectomy+Colostomy	Epitheloid	No	Gemcitabine+ Carboplatin	NA	NA	NA
9	52	74.0	> 28	1	Hysterectomy+BSO+ BPPLND+Omentectomy+ Appendectomy+Peritonectomy	Epitheloid	No	Refused	3.0	Alive	20.0
10	68	4.4	> 28	1	Hysterectomy+BSO+ BPPLND+Omentectomy+ Appendectomy+Splenectomy	NA	NA	Carboplatin+ Paclitaxel	NA	Alive	3.0
11	56	6.5	> 28	1	Hysterectomy+BSO+ Omentectomy+Appendectomy +Splenectomy	Epitheloid	No	Capecitebine+ Oxaliplatin	3.0	Alive	12.0
12	69	99.5	> 28	1	Hysterectomy+BSO+ Omentectomy+Colostomy +Splenectomy	Biphasic	No	Cisplatin+ Pemetrexed	NA	Alive	0.5

PCI: Peritoneal cancer index; DFS: Disease free survival; OS: Overall survival; BSO: Bilateral salpingoophorectomy; BPPLND: Bilateral pelvic and para aortic lymphnode dissection; *patient who had hysterectomy with bilateral salpingoophorectomy before for benign condition; NA: Not available

patients who had colostomies had a too short follow-up period. To evaluate the result of chemotherapy for one patient explorative laparotomy was performed and for three patients secondary tumour mass debulking surgery was done.

Most patients admitted to the hospital were late stage with wide tumour dissemination and a peritoneal cancer index above 28. Only one patient had a peritoneal cancer index below 28. According to the TGM staging system proposed by Sebbag and Sugarbaker patients were staged as follows -1 patient stage II, 4 with stage III, 5 patients stage IV and for two patients there was unknown lymph node status, but regarding the extent of the disease, they were both stage III or IV. In 6 patients completeness of cytoreductive score below 2 was achieved. After completing of surgery, 5 patients did not have any evidence of metastases, for 2 patients it was not possible to asses the presence of metastases, 2 patients had parenchymal liver metastases, 1 patient had pelvic lymphnode metastases and 2 patients had paraaortic lymphnode metastases. There were 4 patients with a prior surgery score of two; all other patients had surgery only once. Correlations between peritoneal cancer index (0.25, p=0.67), prior surgical score (-0.45, p=0.37), completeness of cytoreduction score (0.61, p=0.27) and overall survival were not observed.

For three patients neoadjuvant chemotherapy was given and tumour debulking surgery was performed after the third cycle For three patients cisplatin in combination with Pemetrexed (ALIMTA, manufactured by Eli Lilly and Company, Indianapolis, United States) was given as a first line chemotherapy. For two

patients cisplatin in combination with gemcitabine was given as a first line chemotherapy. For three patients chemotherapy was not completed - one discontinued because of poor performance status, one patient refused and one died after the fifth cycle of gemcitabine and carboplatin. One patient received second line chemotherapy of cisplatin and gemcitabine following the first line chemotherapy of cisplatin and pemetrexed and for one patient chemotherapy was repeated six times with 6 cycles each time. For the last patient, cisplatin with paclitaxel was given as a first line chemotherapy, six cycles of topotecan was received in a second line chemotherapy; etoposide, docetaxel and liposomal doxorubicin were applied as third line chemotherapy agents. Then chemotherapy was continued with carboplatin and liposomal doxorubicin, then gemcitabine as a single agent and after that cisplatin with pemetrexed. As a palliative chemotherapy cyclophosphamide 50 mg a day with metotrexate 2.5mg 2 days a week was ordinated. Overall survival of a particular patient was 100 months.

Information regarding the clinical outcome was available for 9 of our 12 cases, with a mean disease free survival of 4.4±1.0 months after completing a particular treatment and 1-year overall survival of 85.7%.

By the end of the study three patients were dead and six were still alive.

Discussion

Malignant mesothelioma of the peritoneum is a rare disease. Despite the fact that there are no specific symptoms for malignant peritoneal mesothelioma, in the literature similar data for occurrence of abdominal distension in 56% of patients suffering from malignant peritoneal mesothelioma have been reported (14). Abdominal distension was also the most commonly observed symptom, accounting for 75.0% in our study. Manzini reported patients complaining most often about abdominal pain, comprising 35% of patients (15). We observed abdominal pain in 58.3% of our patients and for one third of patients abdominal pain was observed together with abdominal distension. Ascitis was observed in a very high proportion of patients -81.8%, whereas in the literature there are reports of ascitic collection in 36-90% of cases (16-18). This difference may be explained by an investigation method and the amount of abdominal fluid to be considered as pathologic. According to our data, mean time from first symptoms to diagnosis was 1.9 months. Other authors have reported a time interval of 122-180 days from first symptoms (15, 16). Those data indicate a rather large time interval between first symptoms and diagnosis, therefore there is still a place to improve diagnostic techniques that would lead to faster diagnostic and better cure rates.

The small number of cases precludes a uniform therapeutic approach (19). The most common treatment strategy for peritoneal mesothelioma involves a multimodality approach with surgical debulking followed by systemic and/or intraperitoneal chemotherapy. It has been observed that completeness of cytoreductive score below 2 is associated with improved survival and it is the most significant prognostic factors (13). In our study completeness of cytoreduction score below 2 was achieved for 6 patients, but no benefit or improved survival was observed over these who had cytoreductive score for completeness of 2 or higher (0.61, p=0.27 for OS and -0.25, p=0.63 for DFS). There are reports that all patients with lymph node metastases die within 2 years (20). In our study 5 patients had lymphatic or parenchymal metastases. Two of them died, two patients are alive after 20 and 23 months following the diagnosis and there is no information about one other patient who had lymph node metastases.

Regardless of improved survival rates of hyperthermic intraperitoneal chemotherapy, systemic chemotherapy is still given in most oncogynaecologic centres. For three patients neoadjuvant chemotherapy was given and tumour debulking surgery was performed after the third cycle. For one patient neoadjuvant chemotherapy of carboplatin and paclitaxel was given because this case was misdiagnosed as bulky ovarian cancer. Cisplatin in combination with pemetrexed was applied as a first line chemotherapy for three patients, nonetheless no particular chemotherapy regimen correlated with prolonged disease free survival (0.09, p=0.85) or overall survival (0.26, p=0.58) when compared to other chemotherapy regimens. In the literature, the response rates are significantly higher for patients treated with the pemetrexed in combination than for patients treated with cisplatin alone (41% versus 17%, p<0.0001). Patients treated with pemetrexed and cisplatin have also a significantly longer progression free survival (5.7 versus 3.9 months, p=0.001) and overall survival (12.1 versus 9.3 months, p=0.02) when compared to cisplatin alone (21).

Several studies have observed tumour response rates of between 16-48% for gemcitabine used in combination with cisplatin (23-25). Three patients from our study received cisplatin in combination with gemcitabine. There was a trend for shorter overall survival for these patients receiving cisplatin with gemcitabine when compared to other regimens, although the difference was not statistically significant (mean 13.2 vs. 21.2 months, p=0.59).

Another chemotherapy regimen described in the literature discloses a response rate of 26% when gemcitabine is used in combination with carboplatin (26). According to available data, this combination has lower response rates than a combination of gemcitabine and cisplatin.

In the literature there are few articles about topotecan administration for patients with mesothelioma. In a study of patients evaluated with unresectable tumours, the topotecan administered for palliative purposes reported no objective responses with 18 patients having stable disease for a median of 74 days. The median survival for all patients was 230 days, with 23% alive at 1 year (27).

One patient from our study received six cycles of topotecan as a second line treatment, after which chemotherapy was continued in a third line with liposomal doxorubicin, docetaxel and etoposide. In a study of 33 patients receiving lyposomal doxorubicin, 31 patients were evaluable for response and only two patients had a partial response with a median survival of 13 months for all the study patients (28). One patient with a variety of repeated chemotherapy cycles had an overall survival of 100 months. That may indicate the efficacy of repeated

chemotherapy cycles despite the tumour progression. A variety of chemotherapeutic regimens and administration routes with corresponding survival rates are displayed in Table 2.
Of the five patients with a cytoreductive score for completeness of 2 or higher there was available information regarding only two patients, of whom one was dead and another was still alive after 23 months from diagnosis.

Conclusion

Because of the low number of patients and different treatment approaches, data from a particular patient setting are inconclusive, but from the literature there is evidence that patients with malignant intraperitoneal mesothelioma should undergo optimal cytoreduction and receive a combination of cisplatin and pemetrexed as a first line chemotherapy for intravenous or cisplatin in different chemotherapy regimens using the intraperitoneal administration route, if accessible, with even higher overall survival rates.

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Conflict of interest
No conflict of interest was declared by the authors.

Table 2. Summary of trials reflecting different chemotherapeutic agents, route of administration, overall (OS), disease free survival (DFS) and ongoing trials

Study	Patients n	Route of administration	Chemotherapeutic agents and patients in study arms	Median OS, months	Median DFS, months	1-year survival	2-year survival	3-year survival	5-year survival
Vogelzang et al., 2003 (21)	456	I.V.	Pemetrexed+ Cisplatin (226)	12.1	5.7	50.3%	-	-	-
			Cisplatin (222)	9.3	3.9	38.0%	-	-	-
Feldman et al., 2003 (28)	49	HIPEC	Cisplatin+ Fluorouracil+ Paclitaxel	92.0	17.0	86.0%	77.0%	59.0%	59.0%
Jänne et al., 2005 (29)	73	I.V.	Pemetrexed (32)	8.7	-	0.0%	-	-	-
			Pemetrexed+ Cisplatin (66)	13.1	-	66.0%	-	-	-
Yan et al., 2006 (30)	62	HIPEC+EPIC	Cisplatin+ Doxorubicin+ Paclitaxel	79.0	- -	84.0%	-	58.0%	50.0%
Yan et al., 2006 (20)	100	HIPEC+EPIC	Cisplatin+ Doxorubicin+ Paclitaxel	52.0		78.0%	64.0%	55.0%	46.0%
Elias et al., 2007 (31)	22	HIPEC	Oxaliplatin (10) Oxaliplatin+ Irinotecan (12)	100.0	40.0	88.0%	83.0%	68.0%	63.0%
Simon et al., 2008 (22)	20	I.V.	Pemetrexed+ Gemcitabine	26.8	-	67.5%	50.0%	-	-
Hesdorffer et al., 2008 (32)*	27	HIPEC+I.V.	Cisplatin+ Mitomicin+ Doxorubicin	70.0	-	-	-	67.0%	-
Carteni et al., 2009 (33)	109	I.V.	Pemetrexed (38)	10.3	6.2	41.5%	-	-	-
			Pemetrexed+ Cisplatin (37)	-	-	57.4%	-	-	-
			Pemetrexed+ Carboplatin (34)	-	-	-	-	-	-
Blackham et al., 2010 (34)	34	HIPEC	Mitomycin (19)	10.8	8.3	47.0%	47.0%	42.0%	16.0%
			Cisplatin (15)	40.8	10.6	80.0%	80.0%	80.0%	-

I.V.: Intravenous, HIPEC: Hyperthermic intraperitoneal chemotherapy, EPIC: Early postoperative intraperitoneal chemotherapy, *: Additionally receiving radiation therapy

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