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A retrospective analysis of malignant pleural mesothelioma patients treated either with chemotherapy or best supportive care between 1990 and 2005
A single institution experience

Muzaffer Metintas[a,*], Guntulu Ak[a], Sinan Erginel[a], Fusun Alatas[a], Huseyin Yildirim[a], Emel Kurt[a], Selma Metintas[b]

[a] *Department of Chest Diseases, Osmangazi University Medical Faculty, Turkey*
[b] *Department of Public Health, Osmangazi University Medical Faculty, Eskişehir, Turkey*

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Summary The aim of this study was to investigate the efficacy and safety profile of chemotherapy (CT) compared to best supportive care (BSC) in patients with histopathologically confirmed diffuse malignant pleural mesothelioma (DMPM). A total of 161 patients between 1990 and 2004 treated either with CT (109 patients) or BSC (52 patients) depending on patients choice were evaluated in this analyses. Chemotherapy protocols included a combination of cisplatin, mitomycin C and recombinant interferon alpha 2a (CM-In), or cisplatin, mitomycin C and ifosfamide (CMI), or cisplatin and gemcitabine (CG).

We found a significant difference in the median survivals of the patients with CT compared to BSC, 11.3 months versus 8.0. Objective response rate was 28/109 (25.7%) with 3.7% of complete response rate. Stable disease rate was 39/109 (35.8%). There was a significant difference between median survivals of patients with objective response (17 months) and median survivals of patients with progressive diseases (6 months) and also with stable diseases (16 months). There was a significant difference between the stable disease and the progressive disease. Stages 3 and 4 patients of epithelial cell type having received chemotherapy live longer than those not having received chemotherapy (12 months versus 4). There was no significant difference between the survivals of the different chemotherapy regimens. The toxicity with CT regimens were mild and well-tolerated.

Abbreviations: DMPM, diffuse malignant pleural mesothelioma; CT, chemotherapy; BSC, best supportive care; UICC, International Union Against Cancer; IMIG, International Mesothelioma Interest Group; CM-In, cisplatin, mitomycin C and recombinant interferon alpha 2a; CMI, cisplatin mitomycin C and ifosfamide; CG, cisplatin and gemcitabine; KPS, Karnofsky performance score; MS, median survival

* Corresponding author. Tel.: +90 2222392979; fax: +90 2222394714.
E-mail address: metintas@superonline.com (M. Metintas).

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We conclude that CT prolongs survival compared to BSC in patients with DMPM. Survivals of patients with objective response prolong considerably with CT compared BSC. We observed that stages 3 and 4 patients with epithelial cell type got benefit from CT. Especially, of epithelial cell type stages 1 and 2 should receive multimodal treatment.

1. Introduction

Diffuse malignant pleural mesothelioma (DMPM) is a highly lethal neoplasm. In most published series reported median survival for this disease is around 1- and 5-year survival rate is less than 5% [1—4].

Multi-modality treatment regimens slightly prolong survival in small number of patients in whom radical surgery is possible [5,6]. However, only 5% of the patients with DMPM are usually eligible for such a curative surgery at the time of diagnosis [7]. For this reason, most of the DMPM patients are often treated with chemotherapy (CT) or best supportive care (BSC) [8—14]. The overall response rate is around 30% and this is not very satisfactory with CT regimens. Median survival time has not been long enough to justify chemotherapy schedules until recently. Nonetheless, some studies have suggested that mesothelioma may not be totally chemotherapy-resistant and that some chemotherapeutics are moderately effective or tolerable, especially for responders [8—11,13—15]. In addition, combinations of novel chemotherapeutic agents, such as gemcitabine-cisplatin, oxaliplatin-raltitrexed, cisplatin-raltitrexed appeared to give promising results with response rates of more than 30% [16—18]. However, it was determined in these studies that median survival rates of patients receiving chemotherapy were not significantly higher than groups not receiving chemotherapy or receiving some other protocols, thus no clear indications concerning a standard treatment of DMPM had been suggested for CT regimens until the study performed by Vogelzang and colleagues [2,4,8,11,14,15,19—22].

The efficacy of CT in mesothelioma still remains unclear. There is still a lack of solid evidence as to which stage and cell type of patients with mesothelioma could benefit from CT or BSC. Because there are pathological and clinical differences as well as clear differences in terms of prognosis between epithelial cell type and, mixed and sarcomatous cell types [4]. Although it was indicated in studies performed up to now that patients at early phase of epithelial type have benefited from multimodality treatment including surgery, there is no indication regarding whether multimodality therapy will prove beneficial for patients with mixed and sarcomatous cell types [5,6,22]. Some centers even consider these cell types inappropriate for surgery. Again there is no sufficient information yet concerning some other antitumoral treatment activities for this cell type. Still, it is important that new types of therapies, including CT, should be developed for mesothelioma, which is expected to claim the lives of more than 200,000 people in the coming 30 years [23].

Considering the stages and histological types, this retrospective study investigated the survival rates, responses to the treatment, side effects of the treatment of the patients receiving CT or BSC between 1990 and 2005.

2. Materials and methods

2.1. Patient characteristics

Between January 1991 and 2005, 190 patients with histologically proven DMPM were monitored in our clinic with either CT or BSC depending on the choice of the patients. Some of these patients were at early stage and had epithelial subtype; however, they refused to undergo surgery in a multimodality schedule. Of the 190 patients, 121 were given chemotherapy, while another 69 were given only best supportive therapy. However, 161 of a total of 190 patients included in this study were sufficiently followed up in terms of survival rates, responses to chemotherapy and toxicity, thus data of 161 patients were evaluated and presented in this article. Of the 121 patients having CT, 109 patients were found eligible for evaluation with respect to their response to therapy, toxicity and survival rates. The remaining 12 patients were ineligible for response and toxicity due to insufficient follow-up after one course. Sixty-nine of the patients who had been diagnosed at the same period were unwilling to undergo any therapy schedule, and were given BSC. Survival times were determined for 52 of these 69 patients, who were taken as the control group, to compare survival rates with CT group. The other 17 patients could not be followed up as they moved to other places or as we lost contact with them. Data of some of the patients in these series concerning the first CT schedule had already been reported [9]. According to the admission criteria of this study, patients whose KPS was below 70 were excluded from the evaluation process. However, there were a few patients who were incorporated into this group as they were receiving the same schedule.

The characteristics of 161 patients have been presented in Table 1. All the patients were histologically determined to have DMPM. Eligibility criteria for CT and BSC groups were: Hospitalized male and non-pregnant female patients with measurable or evaluable disease; no prior therapy for DMPM (chemotherapy, radiotherapy, intracavitary therapy or surgery); age <80 years; Karnofsky performance score of 70% or greater; adequate serum biochemical profile (bilirubin level < 1.5 times normal, creatinine < 1.5 times normal, creatinine clearance > 60 ml/min); urine analysis; complete blood-cell count (WBC > 4000 mm^{-3}, haemoglobin > 10 g/dl, platelet count > 100,000 mm^{-3}) and clinically normal auditory functions. Patients were excluded if they had significant cardiopulmonary, cerebrovascular, psychiatric and/or renal diseases or peripheral polyneuropathy. Written or verbal informed consents of the patients were obtained prior to their treatments or therapies according to the institutional guidelines.

Following the histopathological diagnosis, the patients were staged according to the International Union Against Cancer (UICC) system by using thoracic, abdominal and brain

Table 1 The features of the patients according to the type of treatment employed

	Chemotherapy	BSC	Total	*P*
Number of patients	109	52	161	
Male/female	55/54	24/28	79/82	0.609
Mean age (years)	57.4 ± 11.1	60.4 ± 12.5	58.3 ± 11.6 (26–80)*	0.116
Asbestos exposure	95/109	41/52	136 (84.5%)/161	0.173
Cell type, *n* (%)				
Epithelial	72 (66.0)	34 (65.4)	106 (65.8)	0.632
Mixed	18 (16.5)	7 (13.4)	25 (15.5)	
Sarcomatous	9 (08.3)	3 (05.8)	12 (07.5)	
Undefined	10 (09.2)	8 (15.4)	18 (11.2)	
Stage, *n* (%)				
I	29 (26.6)	17 (32.7)	46 (28.6)	0.420
II	25 (13.8)	11 (21.2)	26 (16.1)	
III	47 (43.1)	17 (32.7)	64 (39.8)	
IV	18 (16.5)	7 (13.4)	25 (15.5)	
Mean Karnofsky score	79.3 ± 7.8 (70–90)	77.1 ± 8.7 (70–100)	78.6 ± 8.1 (70–100)	0.117
Median survival (months)	11.3 ± 0.9; CI = 9.5–13.1	8.0 ± 0.9; CI = 6.3–9.7	Log-rank = 3.8	0.0508

* Range.

computer tomographic scans, bone scan with TC^{99} and other related tests [24,25]. International Mesothelioma Interest Group (IMIG) staging system were not used for this study, as our patients were started to be admitted to our clinic in 1991. We had already a considerable number of patients until 1995, when IMIG system was begun to be recommended [26]. Although we used the IMIG system for follow-up of the patients beginning in 1995, we used UICC as the key system in this specific report.

2.2. Drug schedule

Regarding chemotherapy protocols used in our clinic, a combination of cisplatin, mitomycin C and recombinant interferon alpha 2a (CM-In) was used as the first protocol between 1990 and 1996. A combination of cisplatin, mitomycin C and ifosfamide (CMI) was used as the second protocol between 1996 and 2000, and another combination of cisplatin and gemcitabine (CG) was used as the third protocol after 2000.

In the first protocol, cisplatin was given 30 mg/m^2 day intravenously (i.v.) on days 1 and 2, mitomycin C 8 mg/m^2 i.v. on day 1 and INF-alpha-2a 4.5 million IU subcutanously twice weekly (days 1, 4, 8, 12, 16, 20, 24, 26). In the second protocol, cisplatin was given 75 mg/m^2 on day 1 i.v., mitomycin C 8 mg/m^2 i.v. on day 1 and ifosfamide 2 g/m^2 i.v. on day 1. In the third protocol, cisplatin was given 75 mg/m^2 day i.v. on day 1, gemcitabine 1250 mg/m^2 i.v. on days 1 and 8.

Chemotherapy cycles were repeated every 28 days in the first protocol, but the frequency was every 21 days for the others. Cisplatin was administered in 500 ml of normal saline over 2 h (with pre and postcisplatin hydration and antiemetics). To prevent nephrotoxicity, pre- and post-cisplatin hydration and diuresis were carried out by administering 1 l of normal dextrose over 2 h, furosemide with each liter of dextrose and 10% mannitol. Emesis was prevented with ondansetron or a combination of metoclopramide and dexamethasone. To prevent a development of fever, paracetamol was used before and after INF applications.

Before each cycle, the patients underwent a complete physical examination, chest X-ray, ECG, respiratory function tests, complete blood count, serum biochemistry and urine analysis. In addition, patients were screened for side effects on 7th and 14th days of the drug administrations. The side effects were graded according to the WHO toxicity scale [27].

2.3. Assessment of response

Lesions were defined as measurable disease, if they could be measured bidimensionally, or accepted as 'evaluable disease' if the tumor size could not be clearly defined.

Response to treatment was assessed subsequent at third cycle of therapy by thoracic CT, and other scans if indicated. Assessment of the response by physicians was not blinded. However, physicians were highly cautious that they were supposed to perform the repeated measurements at the same levels and at least at three separate and anatomically reproducible levels [28].

Complete response (CR) was defined as complete disappearance of all measurable or evaluable lesions, as well as the absence of signs and symptoms for longer than 4 weeks without relapse of lesions. Partial response (PR; for measurable disease) was defined as a decrease in the sum of the products of perpendicular diameters of all measurable lesions greater than 50% compared with pretreatment measurements, and no relapse of lesions over a period of 4 weeks. Regression (for evaluable disease) was defined as an assured decrease in tumor size for lesions not bidimensionally measurable, agreed on by two independent investigators, and no relapse of lesions over a period exceeding 8 weeks. Pleural effusion alone was not accepted as measurable or evaluable disease. Stable disease, both measurable and evaluable, was defined as less

than 50% reduction or less than 25% increase in the sum of the products of the perpendicular diameters of all measurable lesions in relation to the size at entry, over a period exceeding 8 weeks, with no relapse of lesions. For evaluable disease, it was defined as the absence of clear-cut change in an assessable tumor size and the absence of new lesions over a period exceeding 8 weeks. Progressive disease was defined for measurable disease as an increase in the product of two perpendicular diameters of all measured lesions by more than 25% over the initial tumor size at entry, and for evaluable disease as an assured increase in the tumor size. Patients demonstrating a complete or partial response or regression were considered to have given an objective response (OR).

The patients displaying stable disease or an objective response were given six CT cycles, unless there is a tumor progression, death, or unacceptable toxicity.

For response evaluation, we did not use the RECIST (Unidimensional response evaluation criteria in solid tumor) criteria in this study [29]. However, with strong objections being available, the importance of RECIST criteria for chemotherapy response of mesothelioma patients has not been confirmed yet. As the study was started in 1991, a considerable number of cases had already been included in the study before 2000, when RECIST criteria were recommended and the patients were subjected to response evaluation according to criteria employed.

Duration of survival and response was calculated by taking the onset of the treatment as the starting point and the time of death from any cause as the end point.

2.4. Statistical analysis

All analyses were performed using statistical software (SPSS, Version 11.5). Patients' characteristics according to treatment regimen were compared using the Pearson χ^2 test for discrete variables. Duration of survival and median and mean event times, with 95% confidence interval (CI), were estimated according to the Kaplan—Meier method. Differences in time distributions between groups were tested for statistical significance using the log-rank test. The significance level was considered to be 5% ($\alpha = 0.05$) and the approach used was bilateral.

3. Results

Patients ($n = 29$), who died within 2 months of the diagnosis, and those who abandoned the follow-up period early, and a few patients receiving different regimens and those receiving surgical operation was excluded from analysis.

The characteristics of these patients according to treatment arms were shown in Table 1.

We found a statistically significant difference between the median survivals of the patients who received chemotherapy and of those who received best supportive care alone (Fig. 1).

Response rates and median survivals according to response were shown in Table 2.

There was a significant difference between median survivals of patients with objective response and median survivals of patients with progressive diseases (log-rank: 27.4; $P = 0.0000$) and also with stable diseases (log-rank: 5.2; $P = 0.0222$). Likewise, there was a significant difference between the stable disease and the progressive disease (log-rank: 29.7; $P = 0.0000$) (Fig. 2).

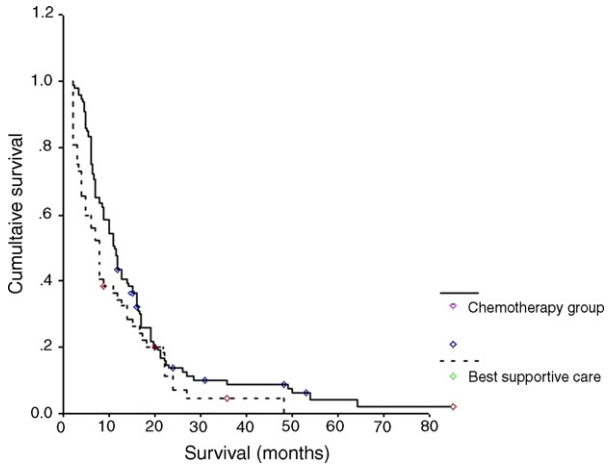

Fig. 1 Kaplan—Meier survival curves for DMPM patients receiving chemotherapy and patients receiving only best supportive care.

Table 2 Response rates and median survivals according to response

Response to therapy	Response rate	Median survival (months)
Objective response	28 (25.7%)	17.0 ± 4.6 (7.9—26.1)
Complete	4 (03.7%)	36.0 ± 13.7 (9.2—62.8)
Partial + regression	24 (22.0%)	16.0 ± 2.7 (10.7—21.3)
Stable diseases	39 (35.8%)	16.0 ± 0.9 (14.3—17.7)
Progressive diseases	42 (38.5%)	6.0 ± 0.3 (5.5—6.5)

12-Month, 2-year and 5-year survival rates of cases have been presented in Table 3.

Survival rates of 12 and 36 months and above in patients receiving CT were found to be higher compared to BSC.

Median survivals of patients receiving CT or BSC according to stages have been presented in Table 4. Median survivals of cases with regard to therapy according to their KPS have been presented in Table 5.

Upon comparing survivals of patients receiving CT and not receiving CT with respect to disease stages, it was determined that there is no significant contribution of CT to survival times in early stage patients; however, it was also determined that patients treated with CT live longer

Table 3 12-, 24-, 36- and 60-month survival rates of patients according to their therapy types

Survival (months)	Chemotherapy, n (%)	Best supportive care, n (%)	Log-rank; *P*
12	52 (47.7)	18 (34.6)	7.82; 0.0052
24	12 (11.0)	5 (9.6)	0.51; 0.47
36	8 (7.3)	2 (3.8)	4.30; 0.0381
60	2 (3.8)	—	

Table 4 Median survivals of patients with regard to stages and cell types according to types of therapy

	Chemotherapy		Best supportive care		Log-rank; *P*
	n	Median survival (range)	*n*	Median survival (range)	
Stages 1 and 2	44	14.0 ± 1.3 (11.4–16.6)	28	11.0 ± 3.9 (3.2–18.8)	0.47; 0.4943
Stages 3 and 4	65	9.0 ± 1.2 (6.7–11.3)	24	5.0 ± 1.0 (2.9–7.0)	10.9; 0.0010
Epithelial					
Stages 1 and 2	28	14.3 ± 2.5 (9.4–19.2)	18	11.0 ± 7.9 (0.0–26.6)	0.00; 0.9870
Stages 3 and 4	44	12.0 ± 1.7 (8.8–15.2)	16	4.0 ± 1.1 (1.8–6.2)	10.0; 0.0016

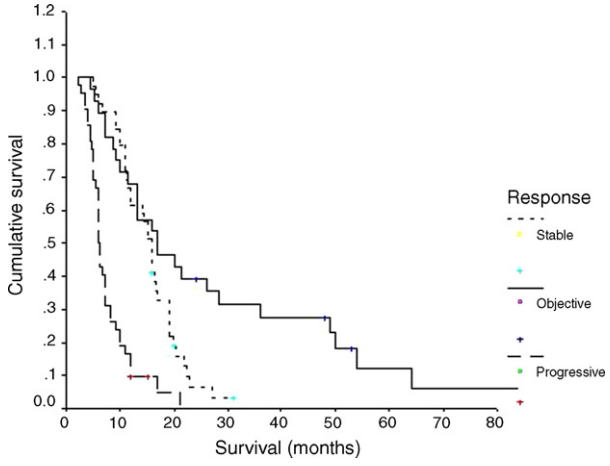

Fig. 2 Kaplan–Meier survival curves for patients receiving chemotherapy according to responses.

than those treated with BSC at advanced stages of the disease (stages 3 and 4). We found that patients with epithelial cell type, CT prolonged survival in stages 3 and 4 patients of epithelial type. Since there were not enough number of patients with cell type of mixed and sarcomatous regarding stages 1, 2 and 3, 4, we did not estimate and compare the median survivals.

Based on the data presented in Table 5, we concluded that KPS was an effective factor in prognosis for all the patients. Whether under CT or not, the lifetime of the patients was observed to increase consistent with the increase in their KPS. There was no change between the lengths of the lifetime of the patients either under the supportive therapy or under CT with low or high KPS. We, therefore, concluded that KPS in itself did not seem to be a determinative factor to be able to determine whether or not CT should be applied.

The features of the patients and their therapy treatment results considering the three CT schedules applied during our study have been presented in Table 6.

There were no significant differences between the median survivals of CT regimens.

3.1. Toxicity

All 109 patients who received CT were assessable for toxicity. The toxicity of these drug combinations was mild and well-tolerated. There were no treatment-related deaths.

Hematologic toxic side-effects have been seen more frequent than others, approximately more than 60% of the patients experienced one or more hematologic side effects at different grades. Myelosuppression was mostly mild to moderate, occurring mostly after the fourth or the fifth cycle. Hematologic complications related to chemotherapy were presented in Table 7. All other system findings related to toxic side-effects have been presented in Table 8.

In the first or second cycles, most patients suffered from prolonged and delayed nausea and vomiting, which affected their daily life quality. However, almost all patients with these symptoms responded well to orally administered ondansetron and the rate of nausea/vomiting decreased in subsequent days by the use of ondansetron intravenously or orally. Other toxic reactions involved: prolonged constipation in 11 patients, anorexia in 10 patients and flu-like symptoms in 12 patients. As a life-threatening toxicity, a pulmonary edema and an encephalopathy occurred in two patients, the first one being after the 3rd and the second after the 2nd chemotherapy course, but both of the patients survived after adequate treatment and support during the first schedule. We were not able to determine why they developed. A mitomycin-induced pneumonitis occurred in a 69-year-old female after the fifth course of her therapy,

Table 5 Median survivals of patients with regard to Karnofsky performance score according to types of therapy

Karnofsky performance score	All patients		Chemotherapy		Best supportive care		Log-rank; *P*
	n	MS*	*n*	MS	*n*	MS	
70	50	6	31	6	19	4	3.31; 0.0688
80	76	11.3	52	12	24	8	3.46; 0.062
90	35	18	26	15	9	22	0.33; 0.56

MS: median survival (months).
* There was a significant difference between median survivals considering KPSs for all patients; log-rank: 36.55; $P = 0.000$.

Table 6 Characteristics of patients and results of treatments according to three chemotherapy regimens

Features	CM-In	CMI	CG	*P*
Number of patients	44	35	30	
Mean age (years)	55.8 ± 10.2	57.2 ± 12.4	59.8 ± 10.6	0.209
Male/female	21/23	21/14	13/17	
Mean Karnofsky score	79.5 ± 7.1	78.9 ± 8.7	79.3 ± 7.8	0.460
Cell type	28.8.5.3	22.6.2.5	22.4.2.2	0.874
Stage				
I	18	4	7	0.106
II	7	6	2	
III	14	19	14	
IV	5	6	7	
Median survivals (months)	11.3 ± 1.7; CI = 8.1—14.6	11.0 ± 1.7; CI = 7.6—14.4	12.0 ± 2.1; CI = 7.9—11.6	0.57
Response rate (%)				
Objective	10 (22.6)	8 (22.9)	10 (33.3)	0.378
Complete	*2 (4)5*	—	*2 (6)7*	
Partial + regression	*8 (18)1*	*8 (22)9*	*8 (26)7*	
Stable disease	18 (40.9)	13(37.1)	8 (26.7)	0.655
Progressive disease	16 (36.5)	14 (40.0)	12 (40.0)	

CM-In: cisplatin + mitomycine + interferon; CMI: cisplatin + mitomycine + ifosfamide; CG: cisplatin + gemcitabine.

Table 7 The number of the patients with specific hematologic toxicities according to chemotherapy schedules[a]

Toxicity	Grade 1			Grade 2			Grade 3			Grade 4		
	I	II	III	I	II	III	I	II	III	I	II	III
Neutropenia	5	2	5	5	3	3	2	4	1	—	2	1
Anemia	13	8	11	12	8	5	1	1	1	—	—	—
Thrombocytopenia	2	3	3	1	2	1	—	2	2	—	2	2

I: the first chemotherapy schedule (cisplatin—mitomycine—interferon); II: the second chemotherapy schedule (cisplatin—mitomycine—ifosfamide); III: the third chemotherapy schedule (cisplatin—gemcitabine).
[a] Only the highest WHO grade is reported for each patient.

Table 8 The number of the patients with non-hematologic toxicities according to chemotherapy schedules[a]

Toxicity	Grade 1			Grade 2			Grade 3			Grade 4		
	I	II	III	I	II	III	I	II	III	I	II	III
Nause/vomiting	18	1	2	10	1	3	10	3	5	—	—	—
Fever	18	—		14	—	—	—	—	—	—	—	—
Nephrotoxicity	11	4	9	1	—	2	—	—	—	—	—	—
Diarrhea	4	—	1	2	—	—	—	—	—	—	—	—
Allopecia	8	—	—	1	1	—	—	—	—	—	—	—
Infection	1	2	—	—	—	—	—	—	—	—	—	—
Ototoxicity	—	—	1	—	—	—	—	1	—	—	—	—
Neurotoxicity	—	1	1	—	—	2	—	—	—	—	—	—
Constipation												
Pulmonary eodema												
Encephalopathy												
Pnomonitis												
Anorexia												

I: the first chemotherapy schedule (cisplatin—mitomycine—interferon); II: the second chemotherapy schedule (cisplatin—mitomycine—ifosfamide); III: the third chemotherapy schedule (cisplatin—gemcitabine).
[a] Only the highest WHO grade is reported for each patient.

but was able to be reversed by discontinuation of this drug and administration of a short-course oral steroid therapy.

4. Discussion

Although mesothelioma is a rare disease, the incidence of DMPM is still increasing and is expected to increase due to abundant inhalation of asbestos fibers in the near past for developed countries [4,23,30]. This trend will probably continue in many developed countries until the second decade of the 21st century due to the long latency period (about 40 years) [31]. On the other hand asbestos exposure is still present in developing countries and legislations are not adequate to achieve sufficient control. In those countries, mesothelioma will continue to pose a health threat during the few decades beyond 2020. Therefore, further investigations of various therapeutic modalities should be tested for their effectiveness in mesothelioma, for which therapeutic success is still unsatisfactory [9,32,33].

Just a few years ago, although almost every chemotherapeutic agent had been tested against DMPM both as single agents and in combination chemotherapy regimens, rates of objective tumor regression were reported under 30% with no significant improving on median survival [8—11,13—15]. Therefore, DMPM was considered relatively resistant to chemotherapy and no regimen was accepted as standard for treatment of DMPM. However, until recently chemotherapy for DMPM continued to be a subject for research [9,14,32], because there was need for new drugs in the treatment of this disease due to its raising incidence. Firstly, it was realized that DMPM was not totally chemotherapy resistant [9,14]. Next, it was realized that the combinations with novel chemotherapeutic agents appeared more promising [8,16—19]. Finally, in a randomized multricentric study, pemetrexed produced a response rate of 45% with an objective improvement in median survival and quality of life in combination with platinum compounds [19]. Pemetrexed use in DMPM was approved by FDA thanks to the results of this study. A drug was given approval for use with mesothelioma for the first time. After this study, some authors claimed that pemetrexed—cisplatin could become the standard chemotherapy regimen for mesothelioma [19,32].

In our previous study, a combination of CM-In combination was moderately effective and well-tolerated, especially by responders [9]. The median survival time was 12 months for stage 1 disease and 16 months for stage I epithelial cell type. The median survival time of the patients with OR was 21.3 months. The patients with OR had significantly longer survival times than non-responders and the patients who BSC [9].

After these encouraging results, we administered chemotherapy with available combinations or BSC (depending on patients choice) to patients who were not eligible for surgical operations or who did not accept surgical treatment after being informed about their disease and the course of their disease. It was worthwhile to examine and publish the results as the number of the patients fully followed by the treatment reached 161, which was considered to be an adequate enough number. As a result, the median survivals of 109 patients followed by chemotherapy were found to be 11.3 months, which was significantly longer than those followed by best supportive care (8 months). This result was the one of the initial studies in which survival time of chemotherapy patients was found to be longer than that of the control group including a high number of patients. However, selection of the patients in this study was not performed by randomization, because the principal thing was the decision of the patient after he/she was aware of the course of the disease. As may be seen in Table 1, in our study data relating to the group receiving best supportive care, which was taken as a control group, was comparable to that of the group receiving chemotherapy.

Evaluation of systemic chemotherapy in DMPM has been problematic for several reasons: (1) this is a rare disease; (2) only a few randomized studies are available; (3) randomization is problematic (will randomization still be ethical if best supportive therapy is applied to one of the groups?); (4) the number of the patients in trials is mostly small; (5) inadequate imaging procedures for response evaluation, therefore non-uniform and unsatisfactory response criteria; (6) non-uniform staging system; (7) clinical trials of DMPM patients included heterogeneous groups of patients with respect to stage and histological subtypes [8]. We think that some data obtained from our study group may be worth discussing and our study is free from some of the above-mentioned limitations.

In our series, out of the group all receiving chemotherapy, 4 patients (3.7%) were with complete response, 25.7% with objective response and 35.8% with stable disease. Median survivals of patients with objective response are longer than patients with stable disease, Median survival of patients with objective response is 17 months and this period of time is considerably longer (more than twice) than 6 months which is for progressive patients and 8 months which is for patients receiving BSC. This distribution shows that the response is a predictor of survival.

One important result of this analysis is that the contribution of chemotherapy to survival times is inversly depend on the disease stage. We could not find any correlation between survival and CT for stages 1 and 2 patients. However compared to BSC, CT at stages 3 and 4 patients lived longer compared to BSC. According to our results we think that this feature was due to the epithelial cell type (Table 4). We found that patients with epithelial cell type, CT does not significantly prolong median survivals in stages 1 and 2 however CT prolonged survival in stages 3 and 4 patients of epithelial type. This result should be considered important due to high number of patients. Median survival of stages 1 and 2 patients of epithelial cell type was found 14.3 months and that of stages 3 and 4 was found 12.0 months.

Multi-modality treatments slightly prolong survival for relatively few patients in whom it is possible to perform radical surgery and about 15% of these patients survive beyond 5 years [6,7,22,34,35]. In their excellent study Rusch and Venkatraman found that median survivals after surgery including adjuvant therapy were 29.9 months for stage 1 disease, 19 months for stage 2, 10.4 months for stage 3 and 8 months for stage 4 [35].

These studies and our results clearly show that multimodality therapies should be applied to only stages 1 and 2 mesothelioma patients of epithelial type. However, it is also

clear from the results of our study that CT will be beneficial for stages 3 and 4 patients of epithelial type. CT should be given to epithelial type stages 3 and 4 patients unless there is a special case or patient's decision. The reason is that, median survival of those receiving chemotherapy in our series (12 months) is significantly higher than that of those receiving best supportive care (4.0 months) and besides the number of patients tested is 44 to 16 as may be seen in Table 4.

The number of patients, with sarcomatous and mixed type, is only 37 (12 sarcomatous and 25 mixed). Although this number is adequate for statistical analyses, it has some margin for error. Further studies with high number of patients are needed to evaluate efficacy of CT for mixed and sarcomatous cell types.

In some recent studies, it was claimed that it would be appropriate to apply chemotherapy to patients with the good prognosis [8]. However, CT did not affect the MS of patients with low or high KPS in our series. In fact, KPS itself indicates good prognosis for all patients. Since patients with objective responses live considerably longer than those with progressive diseases and considering the fact that the objective response rate is below 30% in mesothelioma, we may ask: Is it possible to predetermine the chemotherapy response of patients from some specific clinical and laboratorial parameters? In other words, can we predetermine the patients who may benefit from this toxic and expensive therapy regimen and apply the therapy to those patients? It would be very advantageous to be able to find some useful parameters.

The limitation of our study is the control group, patients receiving BSC, has not been selected by randomization. However, basic characteristics of both groups like age, gender, stage and KPS allow the therapy results of groups to be compared. This fact may overcome this limitation.

Toxicities associated with our treatment regimens schedules were tolerable. There were no toxic deaths. The patients who were experienced toxic side effects were all managed by adequate supportive care.

In conclusion, we observed that response to CT is moderate in mesothelioma patients, but survival of patients receiving CT is higher than BSC. We also observed that CT may prolong survival in patients with objective response. Thus, as a general fact we may state that mesothelioma is not a chemotherapy resistant tumor and that some patients may benefit from chemotherapy. Our findings suggest that chemotherapy does not prolong survivals of patients with early stage epithelial cell type. Therefore, the multimodality treatments including surgical treatment should first be preferred for patients with early stage epithelial cell type. We observed that patients with advanced stage epithelial type tumors significantly benefited from CT. As a result, CT should be recommended as a therapy option to this group. It would not be proper to perform such an evaluation on patients with mixed and sarcomatous type tumors as the number of patients is not sufficient enough. Further studies are needed In addition the following research studies should include control groups, randomization and effective combinations and also studies for determining clinical and biochemical factor/s that may help determine patients who will benefit from chemotherapy should be given priority.

Conflict of interest

None.

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