

Assessment of Survival and Clinical Benefit in Malignant Pleural Mesothelioma (MPM) Patients Treated with Gemcitabine and Carboplatin

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ABSTRACT

Purpose: To evaluate the efficacy, safety, and clinical benefit of combined gemcitabine and carboplatin in patients with previously untreated malignant pleural mesothelioma (MPM).

Patients and Methods: This prospective phase II study was performed on 42 eligible patients with histologically or cytologically proven MPM presenting to Ain Shams University hospitals and Sohag Cancer Center between January 2002 and April 2006. They were assigned to receive combined gemcitabine (1250mg/m²) on days, 1 and 8 and carboplatin (AUC 6) on day 1. The regimen was repeated every 21 days. The treatment continued until disease progression or intolerable drug toxicity.

Results: The patients received a total of 227 cycles of chemotherapy (median 5.4 cycles and range from 2 to 9 cycles). The chemotherapy was generally well tolerated. Neutropenia, thrombocytopenia and anemia were the most severe (Grade 3 or 4) toxicities recorded during therapy and were reported in (14%), (9.5%), and (9.5%), respectively. Twelve patients (29%) achieved partial response, 18 patients (42%) had stable disease and the disease progressed in the remaining 12 patients (29%). The median follow-up duration was 11 months (range 5 from 20 months). The overall survival (OS) and progression free survival (PFS) at one year was 44.5% and 33.2%, respectively. The median survival and time to disease progression were 11 months and 8.5 months respectively. Of 32 patients assessed for clinical benefit, 20 patients (62.5%) were considered clinical benefit responders.

Conclusion: The combination of gemcitabine and carboplatin is a safe and tolerable treatment with reasonable

response rate, OS, and PFS compared with the historical phase II single agents and combined chemotherapy studies in patients with MPM.

Key Words: Mesothelioma – Gemcitabine – Carboplatin.

INTRODUCTION

In Egypt, malignant pleural mesothelioma (MPM) is uncommon but increasing in incidence, particularly in regions where occupational exposure to asbestos has been prominent [1]. MPM is a locally invasive and rapidly fatal malignancy causing death by progressive respiratory failure. At diagnosis, the majority of patients are surgically unresectable. In addition many patients suffer from increasingly severe pain, dyspnea, anorexia, weight loss and weakness as the disease progresses [2].

Currently, there is no gold-standard treatment regimen for MPM. A small proportion of patients (1-5%) are suitable for surgical management. Evaluation of systemic chemotherapy in MPM has been challenging. Anthracyclins (doxorubicin), antimetabolites (high dose methotrexate), and platinum are the most extensively studied individual agents with response rates of 15%, 37% and 16%, respectively [3]. Regimens involving combinations of agents have been similarly disappointing and have shown no clear advantage over single agent therapy. Berghmans et al., [4] published a systematic review of the literature with meta-analysis and suggested that the most active chemotherapeutic regimen, in term of antitumoral response rate, is the cisplatin combinations.

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Gemcitabine, a pyrimidine antimetabolite, was evaluated as a single agent in patients with MPM in three phase II trials with response rates of 0%, 7% and 31%, respectively [5-7]. Although gemcitabine may have a limited role as a single agent, its response rates were improved when it was combined with cisplatin but, unfortunately, the combination was associated with 30% grade 3/4 toxicity profile [8]. Carboplatin is an analogue of cisplatin, which has been developed and studied because of its favorable toxicity profile. It has been studied in patients with MPM with modest response rates of 5% to 16% [9-11]. This finding coupled with the improved toxicity profile and ease of administration compared to cisplatin makes carboplatin an interesting choice to be combined with gemcitabine in patients with MPM aiming to evaluate overall survival (OS) as the primary end point of the study and progression free survival (PFS), response rate, toxicity profile, and clinical benefit as the secondary end point of the study.

PATIENTS AND METHODS

This prospective phase II study was performed on 42 patients with histologically or cytologically proven MPM presenting to Ain Shams University hospitals and Sohag Cancer Center between January 2002 and April 2006. Before entry into the study, all patients underwent a full history and physical examination. Complete blood count with differential, kidney function (creatinine) and liver functions (bilirubin, transaminases and alkaline phosphatase) were assessed. Chest X-ray and computed tomographic (CT) scans of the chest and abdomen were performed as baseline investigations in all patients. Additional imaging investigations were performed if clinically indicated. The eligibility criteria included: (a) performance status of ≥ 50 on Karnofsky scale [12] (b) no prior chemotherapy or radiotherapy, (c) adequate bone marrow (leucocyte count $\geq 4000/\mu\text{L}$, absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$ and hemoglobin $\geq 10\text{g/dl}$), (d) adequate kidney function (creatinine $< 1.5\text{mg/dL}$) (e) adequate liver functions (bilirubin $< 2\text{mg/dL}$, and transaminases levels < 3 times the upper normal limit [five times for patients with liver metastasis]). Patients were staged according to the International Mesothelioma Interest Group (IMIG) [13].

Treatment plan:

The chemotherapy regimen consisted of gemcitabine and carboplatin and was repeated every 21 days. The treatment continued until there was clinical or radiological evidence of disease progression or intolerable drug toxicity. The dose of gemcitabine was 1250mg/m^2 on day 1 and 8. The drug was diluted in 200ml normal saline and administered intravenously over 30 minutes. Carboplatin was administered on day 1 after gemcitabine as a 30-minute intravenous infusion in 500ml of normal saline. The carboplatin dose was calculated according to the Calvert formula with an area under the plasma concentration curve (AUC) of $6\text{mg/ml} \cdot \text{min} \times (\text{glomerular filtration rate} + 25)$ using a calculated glomerular filtration rate from the Cockcroft Gault formula. Each chemotherapy cycle could only start if the ANC and platelet counts on the day of treatment were $\geq 1500/\mu\text{L}$ and $\geq 100,000/\mu\text{L}$, respectively. Treatment was delayed until this level was achieved and if the delay was longer than 2 weeks, the patient was taken off the treatment.

Follow-up studies:

Complete blood count with differential, creatinine level, liver functions and chest X-ray were performed every 3 weeks before each cycle of chemotherapy. A thoracic CT scan was repeated every 3 cycles of chemotherapy to assess tumor response. After that, CT thorax was repeated every 3 months for the first year and then every 6 months. Additional laboratory or imaging investigations were performed if clinically indicated.

Toxicity:

All signs, symptoms or laboratory abnormalities were assessed using the WHO criteria for toxicities [14]. Change in the disease was assessed by measuring the thickness of up to three involved areas of pleural rind at each of three separate levels at least 2cm apart on CT scan, at least one measurement was $> 1.5\text{cm}$.

Assessment of the response:

Tumor response was evaluated according to the Modified RECIST (Response Evaluation Criteria In Solid Tumors) [15]. For unidimensional lesions, the thickness of the tumor (pleural rind) perpendicular to the chest wall or mediastinum was measured in two positions at three separate levels on transverse cuts of the

CT scan. Transverse cuts should be at least 1cm apart and related to anatomical landmarks in the thorax. Complete Response (CR) was defined as disappearance of all known disease. Partial Response (PR) was defined as a >50% decrease in the sum of the products of perpendicular diameters of bidimensionally lesions or >30% decrease in the sum of linear tumor measurements for unidimensional lesions. Progressive disease (PD) means a >25% increase in the size of the tumor for bidimensional lesions or >20% increase in the sum of linear tumor measurements for unidimensional lesions or the appearance of new lesions. Patients with stable disease (SD) were those who fulfilled the criteria for neither CR, PR nor PD. All tumor measurements should be on two observations not less than 4 weeks apart.

Statistics:

The Kaplan-Meier method was used for the calculation of the OS and the PFS. Survival was estimated from the date of first treatment to death or last follow-up visit. Time to tumor progression was estimated from the date of first treatment to first evidence of disease progression. Fisher exact test was used to compare

independent proportions. p value ≤ 0.05 was considered statistically significant.

Clinical benefit:

Clinical benefit assessment is based on measurement of three common debilitating signs or symptoms present in most patients with advanced malignancies, including pain (assessed by pain intensity and analgesic consumption), functional impairment (assessed by Karnofsky performance status), and weight loss (Table 1) [16]. The pain intensity score ranged from 0 (least possible pain) to 100 (worst possible pain) on the visual analogue scale [17]. Pain and functional impairment were considered primary measure. Weight change was considered a secondary measure. A patient was considered assessable for clinical benefit if, before entry onto the study, he or she presented any of the following: A pain score of more than 20 on the Memorial Pain Assessment Card visual analog scale, consumption of more than 10 morphine-equivalent milligrams of analgesia/day, performance status of 70% or lower on Karnofsky scale, and weight loss of more than 10% in the previous 6 months. The patient was assessed for clinical benefit at each visit during chemotherapy and then during follow-up.

Table (1): Classification for clinical benefit measures [16].

Primary measures:	
A- Pain:	
Pain intensity	Measured on the MPAC* 0-100 visual analogue scale
Positive	A more than 50% improvement from baseline for 4 weeks or longer
Negative	Any worsening from baseline sustained for at least 4 weeks.
Stable	Any other result
Analgesic consumption	Measured in morphine-equivalent milligrams
Positive	A decrease of >50% from baseline sustained for 4 weeks or longer.
Negative	Any worsening from baseline sustained for at least 4 weeks.
Stable	Any other result
B- Karnofsky performance status:	
Positive	An improvement of >20 points from baseline, sustained for >4 weeks
Negative	Any worsening of >20 points from baseline, sustained for >4 weeks
Stable	Any other result
Secondary measures:	
Weight:	
Positive	A weight gain of >7% from baseline, sustained for >4 weeks
Negative	Any other result

* MPAC = Memorial Pain Assessment Card Visual Analog scale.

A patient was considered to be a clinical benefit non-responder by the primary measures of response if either pain or Karnofsky performance scale (KPS) was classified negative. If either the pain or performance status measures were positive, a patient was identified as a clinical benefit responder. If pain and performance status were both stable, the patient was considered a clinical benefit responder if he experienced a positive change in weight. A patient was categorized as clinical benefit non-responder if he was stable on the primary measures and did not experience a non positive change in weight. For a patient to be considered as a clinical benefit responder, at least one component of clinical benefit response must have been positive with none of the other components being negative.

RESULTS

The characteristics of the 42 treated patients are detailed in Table (2). The median age was 49.2 years, and 31 were males. The most common presenting symptoms and signs were chest pain (32 patients), dyspnea (24 patients), and weight loss >10% (11 patients). Thirty patients had performance status of 50-70 on Karnofsky scale. Twenty-five patients had a history of asbestos exposure. Pathologically, 14 patients (33%) had epithelial mesothelioma, 8 (19%) had sarcomatous type, and 13 (31%) had mixed type. The diagnosis was confirmed through cytological examination of the pleural fluid in 7 patients (29%). Thirty three patients were classified as stage II-III and 9 patients had stage IV tumors. The patients received a total of 227 cycles of chemotherapy (median 5.4 cycles and range from 2 to 9 cycles).

Toxicity:

The chemotherapy was generally well tolerated throughout the study. Specific treatment-related toxicities are detailed in Table (3). A total of 11 patients (26%) experienced at least one severe (grade 3 or 4) toxicity. The major toxicity observed was hematologic. WHO grade 3 and 4 neutropenia was recorded in 14% of patients who required medical treatment with broad spectrum antibiotics and granulocyte colony stimulating factors; one of these patients died from septicemic shock. Grade 3 and 4 thrombocytopenia was reported in 9.5% of patients. Grade 3 anemias that required hospital admission and repeated packed red blood cell

transfusion was reported in 9.5% of patients; one of the patients who had grade 4 anemia developed anemic heart failure. All the patients developed mild degree non-haematological toxicity in the form of grade 1 or 2 nausea and vomiting, but only 3 patients (7%) developed WHO grade 3 nausea and vomiting and one patient (2.5%) developed grade 3 diarrhea that necessitated treatment interruption, hospital admission and intravenous fluids. In 6 instances, chemotherapy was stopped after two cycles due to intolerable toxicity (3 patients) or disease progression (3 patients).

Table (2): Patient characteristics.

Parameters	No. of patients (n=42)
<i>Age (years):</i>	
Median \pm SD	49.2 \pm 19
Range	(30-68)
Sex (M/F)	31/11
<i>Symptoms and Signs:</i>	
Pain	32 (76%)
Dyspnea	24 (57%)
Weight loss (>10%)	11 (26%)
<i>Karnofsky performance status:</i>	
50-70	30 (71%)
80-90	12 (29%)
History of asbestos exposure	25 (60%)
<i>Pathology:</i>	
Epithelial	14 (33%)
Sarcomatous	8 (19%)
Mixed	13 (31%)
Malignant mesothelial cells (cytology)	7 (17%)
<i>IMIG Staging system:</i>	
II-III	33 (79%)
IV	9 (21%)

Table (3): Maximum toxicity profile according to WHO criteria for toxicity [14].

Toxicity	Grade 3	Grade 4	Total
Neutropenia	5	1	6 (14%)
Thrombocytopenia	3	1	4 (9.5%)
Anaemia	4	–	4 (9.5%)
Nausea/Vomiting	3	–	3 (7%)
Diarrhea	1	–	1 (2.5%)

Response:

Twelve patients (29%) achieved partial response (PR) (Figs. 1,2). Eighteen patients (42%) had a stable disease (SD) and the disease progressed (PD) in the remaining 12 patients (29%). Three of the progressed patients received second line chemotherapy (high dose methotrexate), the remaining patients were maintained under the best supportive care.

Survival and progression-free survival:

The median follow-up duration was 11 months (range 5-20 months). The OS at one year was 44.5% [95% CI is 29.3 to 59.7%] and

the 1-year PFS was 33.2% [95% CI 18.9-47.5] (Fig. 3 A,B). The median survival and the median time to disease progression were 11 months and 8.5 months, respectively. The main cause of death was progressive respiratory failure.

Table (4) shows the correlation between PR, 1 year OS and median survival with different prognostic factors, sex, performance status, pathology subtype, and IMIG (International Mesothelioma Interest Group) staging system. Only good performance status (80-90) and non metastatic disease had significantly better results.

Table (4): Partial response, 1-year overall survival, and median survival in relation to different prognostic factors.

Prognostic criteria	No	PR	p-value	1 year-survival %	Median survival	p-value
<i>Sex:</i>						
Male	31	9 (29%)		53.0	14.0	
Female	11	3 (27%)	0.912	41.9	11.0	0.9
<i>Performance status:</i>						
80-90	12	8 (75%)		82.5	20.0	
50-70	30	4 (13%)	<0.001	30.0	11.0	0.001
<i>Pathology subtype:</i>						
Epithelial	14	6 (43%)		50.0	12.5	
Sarcomatous	8	2 (25%)		51.9	16.0	
Mixed	13	4 (31%)		50.0	12.5	
Cytology	7	0	0.253	14.3	10.0	0.3

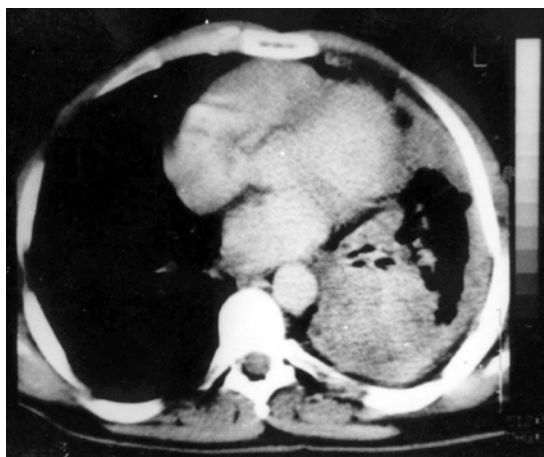


Fig. (1-A): Transverse cut of CT chest of a mesothelioma patient.

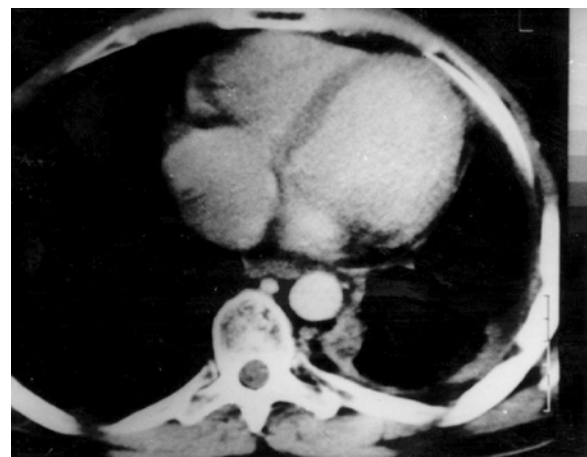


Fig. (1-B): Transverse cut of CT chest of the same patient with partial response.

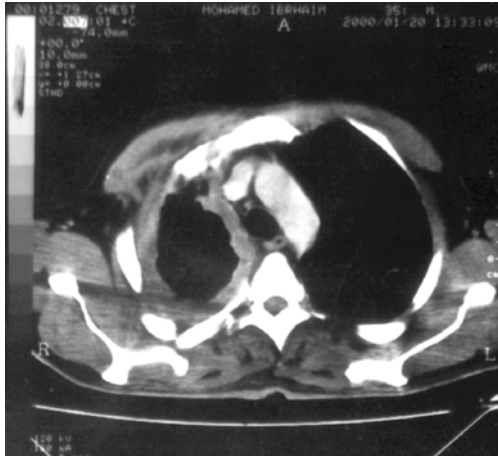


Fig. (2-A): Transverse cut of CT chest of a mesothelioma patient.

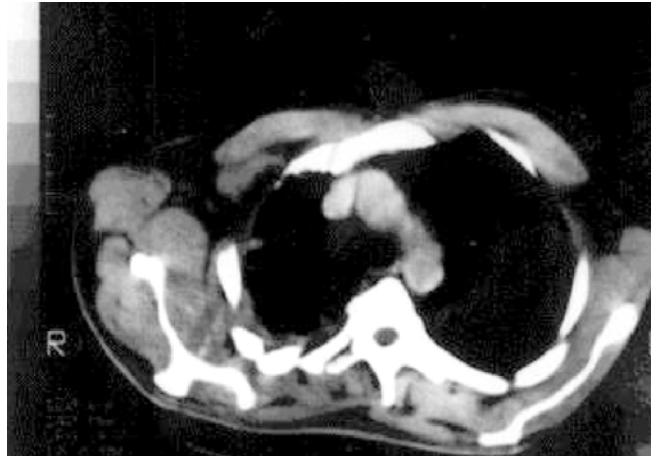


Fig. (2-B): Transverse cut of CT chest of the same patient with partial response.

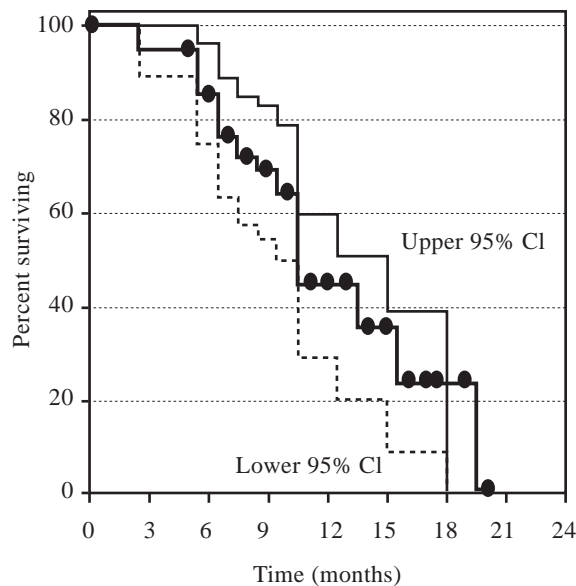


Fig. (3-A): One year overall survival.

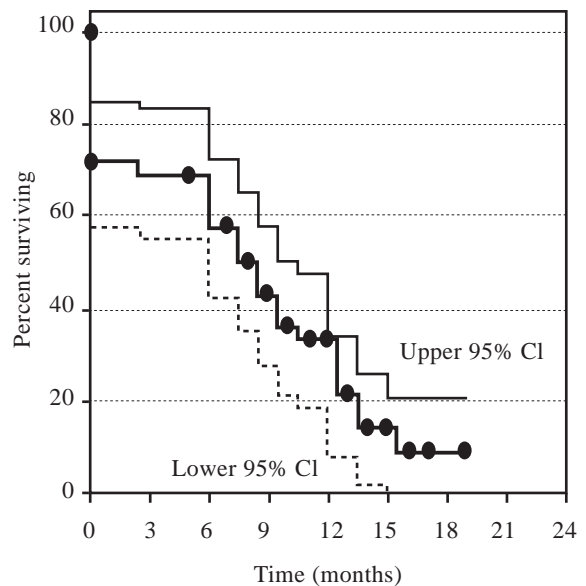


Fig. (3-B): One year progression-free survival.

Clinical benefit:

Thirty two patients (76%) had one or more of the eligible criteria for clinical benefit assessment while 10 patients did not fulfill these criteria. Fifteen patients (36%) had pain at entry (a baseline pain intensity score greater than 20 points or required more than 10mg/day morphine equivalent for control of the pain). A Karnofsky performance status of 50-70% was recorded in 30 patients (71%) while weight loss of more than 10% was recorded in 11 patients (26%). Twenty patients were considered as

clinical benefit responders by the primary measures (pain and functional assessment), 8 patients were considered clinical benefit non-responders because of negative impact on pain and/or functional impairment. The remaining 4 patients were stable by the primary measures criteria. Unfortunately, none of these 4 patients gained >7% of their baseline weight to be considered as clinical benefit responders by secondary measure. This means that twenty patients (62.5%) out of 32 eligible patients were considered clinical benefit responders by primary and secondary measures.

DISCUSSION

A major finding of the current study was an achievement of PR rate of 29% and SD rate of 42% with an overall survival at one year of 44.5% and a median survival of 11 months and manageable toxicity. Aversa et al., [18] treated 20 MPM patients with gemcitabine at 1000mg/m² on days 1, 8, & 15 and carboplatin (AUC=5) on day 1 every 28 days for a median of 4.5 cycles. In 18 assessable subjects, a response rate of 16% and a median survival of 8.6 months were achieved. The discrepancy in the results between the present study and Aversa et al., study may possibly result from the different treatment intensity (4 week schedule in Aversa et al., study Vs. 3 week schedule in the present study). Recently, Rea et al. [19] treated MPM patients with induction chemotherapy, gemcitabine and carboplatin for 3-4 cycles before surgery. They reported, according to modified RECIST criteria, a PR rate of 33% and an SD rate of 66%.

Combination therapy with cisplatin is the mainstay therapy for MPM [4,11]. An Australian study group, evaluated the doublet gemcitabine (1000mg/m² days 1, 8 and 15) cisplatin (100mg/m² on day1) every 28 days in 53 patients with MPM in a multicenter study [20]. A response rate of 33% was achieved and the median survival time was 11.2 months. van Haarst et al. [21] performed another multicenter study to evaluate the doublet, gemcitabine (1250mg/m² days 1 and 8) and cisplatin (80mg/m² on day 1) every 21 days in 25 patients with MPM, a PR rate of only 16% was achieved and the median survival time was 9.6 months. Metintas et al. [22] compared different cisplatin based chemotherapy versus best supportive care for 161 patients with diffuse MPM. There was a significantly better survival and response rates with chemotherapy. The median survival with chemotherapy was 11.3 months, objective response was 26% and SD was reported in 36% of patients. van Meerbeeck et al., [23] treated 250 patients with cisplatin with and without raltitrexed. The median survival and response rate for cisplatin arm were 8.8 months and 13.6% compared to 11.4 months and 23.6% for cisplatin/raltitrexed arm.

Analysis of different prognostic factors for tumor response, and survival showed that good

performance status (Karnofsky 80-90), and non metastatic, stage II and III patients had significantly better response and median survival compared with their counterparts. This is in agreement with several reports in the literature [21,22,24].

A total of 11 patients (26%) experienced at least one severe (grade 3 or 4) toxicity. The toxicity was mainly hematologic. WHO grade 3 and/or 4 neutropenia, anemia and thrombocytopenia, were recorded in 14%, 9.5% and 9.5%, respectively. WHO grade 3 nausea and vomiting were experienced in 7% only of the patients. The overall toxicity seemed to be tolerable and comparable to that reported by Aversa et al., trial [18]. In the Rea et al. trial, hematological toxicity was reported in 38% of patients treated with 3-4 cycles of gemcitabine and carboplatin before surgery [19]. In addition, the toxicity was better than that reported with other two-drug chemotherapeutic regimens especially gemcitabine/cisplatin combination. The Australian group trial, reported grade 3 neutropenia in 38%, grade 3 and 4 thrombocytopenia in 33%, and grade 3 nausea and vomiting in 33% of patients limiting the mean relative dose intensity of gemcitabine and cisplatin to 75% and the total number of chemotherapy cycles to 6 cycles [20]. In the van Haarst et al., trial of gemcitabine and cisplatin, severe toxicity (\geq grade 3) was recorded in 20% of patients [21].

Pemetrexed, an antifolate drug that used alone or in combination with platinum compounds, is the only chemotherapy that is currently licensed in Europe and USA for malignant pleural mesothelioma. Phase I studies had previously shown 32% response rate for patients treated at varying doses and combinations of pemetrexed [25,26]. Phase II studies investigating the use of pemetrexed in combination with gemcitabine, cisplatin, carboplatin and vinorelbine in fully vitamin B12 and folic acid supplemented patients reported PR rates that ranged from 21% to 33% and overall survival that ranged from 10.7 to 14.8 months. Vogelzang et al. [26] performed a phase III trial, and included more than 400 patients, comparing cisplatin alone or in combination with pemetrexed; the response rate was 16.7% in the cisplatin arm versus 41.3% in the combined arm. The median survival and time to progression were 9.3 and

3.9 months, respectively in the cisplatin arm versus 12 and 5.7 months, respectively in the pemetrexed/cisplatin arm. However, pemetrexed was complicated with statistically significant severe G3/4 toxicity even after supplementation with folic acid and vitamin B12. They reported grade 3/4 neutropenia of 23%, and nausea and vomiting of 22%.

Recently, a trimodality therapy consisting of induction platinum-based chemotherapy for 3-4 cycles followed by extrapleural pneumonectomy (EPP) and postoperative irradiation was evaluated by several investigators. However the surgery was associated with high morbidity and mortality rate that reached 35% and 2.5% respectively [19,31]. These results need more confirmation with controlled randomized trials.

A distinctive feature of MPM is the high incidence of significant tumor-related symptoms. So, the reason for the current scrutiny of chemotherapy over best supportive care only for patients with advanced disease is its potential role in the relief of tumor-associated symptoms and improvement of quality of life (QOL). The tool we utilized included three important measures; pain, performance status that reflect the functional impairment and weight loss. This was applied to other advanced malignancies. It may be criticized as it does not include dyspnea assessment which was one of most important significant MPM related symptoms. However, we thought the improvement of dyspnea in these patients must be reflected on their functional status. In the present study, 20 of 32 patients eligible for assessment of QOL (62.5%) were considered clinical benefit responders, i.e they achieved better QOL. The data on health related QOL of MPM patients is relatively sparse using different scales for QOL assessment but unfortunately suffering from poor compliance [26,32-34]. In the Vogelzang et al., trial [26] of cisplatin with and without pemetrexed, the patient's QOL was assessed using a modified lung cancer measure and revealed that the initial three cycles of chemotherapy led to a reduction in global QOL and stabilized at subsequent assessments. Bottomley et al., [34] reported the results of an international randomized European Organization for Research and Treatment of Cancer (EORTC) phase III

study of cisplatin with or without raltitrexed in 250 patients with MPM. The QOL in this trial was assessed with EORTC-QOL questionnaire tools. Although patients in the cisplatin/raltitrexed arm had significant clinically meaningful improvements of dyspnea during treatment and although both groups had impairment of global QOL when compared to a normative population, the levels of QOL items, like pain control, although not deteriorated, but remained stable over the treatment time.

Conclusion: The combination of gemcitabine and carboplatin is a safe and tolerable treatment with reasonable response rate, OS and PFS compared with the historical phase II single agents and combined chemotherapy studies in patients with MPM.

REFERENCES

- 1- Gaafar RM. Malignant pleural mesothelioma: An Overview. In New Perspective in The Management of Lung Cancer. (Abstract) The second NCI-EORTC Lung Cancer Symposium. 2003.
- 2- Robinson BW, Musk AW, Lake RA. Malignant Mesothelioma. *Lancet*. 2005, 366: 397-408.
- 3- Tomek S, Emri S, Krejcy K, Manegold C. Chemotherapy for malignant pleural mesothelioma: Past results and recent developments. *Br J Cancer*. 2003, 88: 167-74.
- 4- Berghmans T, Paesmans M, Lalami I, Louviaux I, Luce S, Mascaux C, et al. Activity of chemotherapy and immunotherapy on malignant mesothelioma: A systematic review of the literature with meta-analysis. *Lung Cancer*. 2002, 38: 111-21.
- 5- Van Meerbeeck Baas P, Debruyne C, Groen HJ, Manegold C, Ardizzoni A, Gridelli C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. *Cancer*. 1999, 85: 2577-82.
- 6- Kindler HL, Millard F, Herndon JE, Vogelzang NJ, Suzuki Y, Green MR. Gemcitabine for malignant mesothelioma: A phase II trial by the Cancer and Leukemia Group B. *Lung Cancer*. 2001, 31: 311-7.
- 7- Korman DB, Boronovskaia LE, Maslova IA. The use of gemcitabine in the treatment of patients with mesothelioma. *Vopr Onkol*. 2006, 52 (4): 461.
- 8- Pinto C, Marino A, De Pangher Manzini V, Benedetti G, Galetta D, Mazzanti P, et al. Sequential chemotherapy with cisplatin/gemcitabine (CG) followed by mitoxantrone/methotrexate/mitomycin (MMM) in patients with malignant pleural mesothelioma. A Multicenter Italian Phase II Study (SITMP1). *Lung Cancer*. 2006, 52 (2): 199-206.

- 9- Baas P. Chemotherapy for malignant mesothelioma from doxorubicin to vinorelbine. *Semin Oncol.* 2002, 29: 62-9.
- 10- Raghavan D, Gianoutsos P, Bishop J, Lee J, Young I, Corte P, et al. Phase II trial of carboplatin in the management of malignant mesothelioma. *J Clin Oncol.* 1990, 8: 151-4.
- 11- Barata F, Cortesao N, Marques A, Figueiredo A. Chemotherapy in malignant pleural mesothelioma. *Rev Port Pneumol.* 2005, 11 (6 Suppl 1): 14-5.
- 12- Karnofsky DA. Adopted from Cancer treatment Medical Guide. Gianni Beretta. 1991, P 18.
- 13- Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group (IMIG). *Chest.* 1995, 108: 1122-8.
- 14- Miller AB, Hoodgraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981, 47: 207-14.
- 15- Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Annals Oncol.* 2004, 15: 257-60.
- 16- Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol.* 1997, 15 (6): 2403-13.
- 17- Coyle N, Layman-Goldstein M. Pharmacologic management of adult cancer pain. *Oncology (Williston-Park).* 2007, 21 (2 Suppl Nurse Ed.: 10-22; discussion 26.
- 18- Aversa SM, Favoretto AG. Carboplatin and gemcitabine chemotherapy for malignant pleural mesothelioma (MPM): A phase II study of the GSTPV. *Clin Lung Cancer.* 1999, 1: 73-5.
- 19- Rea F, Marulli G, Bortolotti L, Breda C, Favaretto AG, Loreggian L, et al. Induction chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant hemi-thoracic radiation in malignant pleural mesothelioma (MPM): Feasibility and results. *Lung Cancer.* 2007, 57 (1): 89-95.
- 20- Nowak A, Byrne M, Williamson R: A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer.* 2002, 87: 491-6.
- 21- Van Haarst JMW, Baas P, Manegold C, Schouwink JH, Burgers JA, de Bruin HG, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer.* 2002, 86: 342-5.
- 22- Metintas M, Ak G, Erginel S, Alatas F, Yildirim H, Kurt E, et al. A retrospective analysis of malignant pleural mesothelioma patients treated either with chemotherapy or best supportive care between 1990 and 2005 A single institution experience. *Lung Cancer.* 2007, 55 (3): 379-87.
- 23- van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, et al. Randomized Phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: An intergroup study of the EORTC Lung Cancer Group and the NCIC. *J Clin Oncol.* 2005, 23: 6881-9.
- 24- Antman K, Shemin R, Ryan L, Klegar K, Osteen R, Herman T, et al. Malignant mesothelioma: Prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's hospital experience over two decades, 1965-1985. *J Clin Oncol.* 1988, 6: 147-53.
- 25- Green MR. Alimta (pemetrexed disodium): A multitargeted antifolate for the treatment of mesothelioma. *Lung Cancer.* 2002, 38 (Suppl 2): S55-7.
- 26- Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003, 21: 2636-44.
- 27- Adjei AA, Erlichman C, Sloan JA, Reid JM, Pitot HC, Goldberg RM, et al. Phase I and pharmacologic study of sequences of gemcitabine and the multitargeted antifolate agent in patients with advanced solid tumors. *J Clin Oncol.* 2000, 18 (8): 1748-57.
- 28- Milward M, Clarke S, Beale P, Boyer M, Childs A, Bishop J. Phase I trial of pemetrexed (Alimta) and vinorelbine in patients with advanced cancer (Abstract). American Society of Clinical Oncology (ASCO) Annual Meeting. 2001.
- 29- Hughes A, Calvert P, Azzabi A, Plummer R, Johnson R, Rusthoven J, et al. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2002, 20 (16): 3533-44.
- 30- Ceresoli GL, Zucali PA, Favaretto A, Marangalo M, Del Conte G, Ceribelli A. A phase II study of pemetrexed and carboplatin as front-line chemotherapy in patients with malignant pleural mesothelioma (MPM). American Society of Clinical Oncology (ASCO) Annual Meeting. 2005.
- 31- Weder W, Stahel R, Bernhard J, Bodis S, Vogt P, Ballabeni P, et al. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. *Ann Oncol.* 2007, 18 (7): 1196-202.
- 32- Hollen PJ, Gralla RJ, Liepa AM, Symanowski JJ, Rusthoven JJ. Adapting the Lung Cancer Symptom Scale (LCSS) to mesothelioma: Using the LCSS-Meso conceptual model for validation. *Cancer.* 2004, 101: 587-95.
- 33- Nowak AK, Stockler MR, Byrne M. Assessing quality of life during chemotherapy for pleural mesothelioma: Feasibility, validity, and results of using the European Organisation for Research and Treatment of Cancer core quality of life questionnaire and lung cancer module. *J Clin Oncol.* 2004, 22: 3172-80.

34- Bottomley A, Gaafar R, Manegold C, Burgers S, Coens C, Legrand C, et al. Short term treatment-related symptoms and quality of life: Results from an international randomized phase III study of cisplatin with

or without raltitrexed in patients with malignant pleural mesothelioma: An EORTC Lung Cancer Group and National Cancer Institute, Canada, Intergroup Study. *J Clin Oncol.* 2006, 24 (9): 1435-42.