Efficacy and tolerability of cisplatinum and adriamycine as combination chemotherapy for Malignant pleural mesothelioma

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Key words: Pleural Mesothelioma, Cisplatin and Adriamycine.

Submitted: March 2010 - Accepted: 30 May 2010

ISSN: 2070-254X

Abstract

Pleural mesothelioma is a locally invasive and aggressive tumor with a poor prognosis . Its incidence is increasing throughout most of the world . Therefore, effective systemic chemotherapy for pleural mesothelioma is clearly needed. This study is prospective phase II study to evaluate the efficacy and tolerability of cisplatinum and adriamycine as combination chemotherapy for malignant pleural mesothelioma

Patients & Methods: Between December 2005 and March 2007 , 30 patients were registered . Eligibility criteria included Karnofsky performance status ≥60 and no prior chemotherapy . Of 30 patients entered , 25 were included , 17 of them have epithelial cell type and 8 with sarcomatous or mixed cell type . Patients received a total of six cycles of adriamycine (50mg/m2) and Cisplatin (80mg/m2) chemotherapy regimen .

Results: Overall response rate was 16%. Stabilization rate including partial response and no change was 56% . Median response duration was 8 months (range 4 – 12 months) . Median overall survival was 12 months (range 7 – 16 months). Performance status was considered a potential prognostic factor for overall survival (**p = 0.04**) . The main toxicities were nausea and vomiting , neutropenia , thrombocytopenia and alopecia . No toxic death was documented .

Conclusion: Combination of cisplatin and adriamycine is active well tolerated chemotherapy with reasonable toxicity for patients with pleural mesothelioma. However, it does not demonstrate superior activity to other active regimens in this disease.

Introduction

Pleural mesothelioma is a tumor derived from the mesothelium covering the surface of pleural membranes or from undifferentiated mesenchymal cells in connective tissue under the membranes. It is a locally invasive and aggressive tumor with a poor prognosis and a median survival time of ≈ 9–16 months (1).

Pleural mesothelioma is known to be linked to asbestos exposure, and the incidence of this tumor is expected to increase in the next 10– 20 years according to an estimation of asbestos consumption in the world . Its incidence is increasing throughout most of the world, and it is predicted that it will rise in the next 10 to 20 years (2).

Surgical resection offers local control of the tumor but its effect on survival remains unclear. In addition, application of radiation therapy is limited because of the diffuse extension of tumor spread. Whole lung radiotherapy has not demonstrated its efficacy in controlling the disease (3). Finally, numerous chemotherapeutic agents have been tested in phase II studies (3). Response rate does not exceed 20% for the majority of the investigated regimens. In narrative reviews, agents such as cisplatin, doxorubicin, high dose methotrexate, alkylating agents or mitomycin C appear potentially active (4,5).

A systematic review was conducted , recently updated, of the fully published literature with a methodological quality assessment of the studies relative to chemotherapy or immunotherapy in malignant mesothelioma (6,7). They aggregated, for similar quality studies, response rates to identify the more active chemotherapeutic drugs and regimens, in order to use the obtained information for future trials. Ninety-five studies (100 treatment arms) were eligible for the systematic review. Overall, they concluded that cisplatin-based chemotherapy, when associated with doxorubicin, etoposide or gemcitabine, presented with significantly better response rate than other chemotherapy regimens and that polychemotherapy was superior to single-agent therapy (7).

Regimens applied to lung cancer such as platinum-containing chemotherapy have been used for MPM in Japan; however, the efficacy outcomes of these therapies are not satisfactory (8).

The European Lung Cancer Working Party (ELCWP) decided to conduct a prospective phase II study assessing the activity of combination chemotherapy that showed that cisplatin plus epirubicin appears as an effective regimen in malignant mesothelioma, with a favorable toxicity profile. However, it does not demonstrate superior activity to other active regimens in this disease (9).

Therefore, effective systemic chemotherapy for MPM is clearly needed.

Recently, Vogelzang et al. demonstrated in a randomized phase III trial that a combination of cisplatin and pemetrexed (Alimta®) was superior to single agent cisplatin both for response rate and survival (10).

Aim of work

- Evaluate the efficacy and tolerability of cisplatinum and adriamycine as combination chemotherapy for malignant pleural mesothelioma .
- Follow up for the toxicity profile of cisplatinum and adriamycine as combination chemotherapy .
- Assess the overall response and quality of life for malignant pleural mesothelioma patients receiving combination chemotherapy .

Patient and methods

This study was conducted from December 2005 to March 2007 in Kaser El-Aini Center of Oncology and Nuclear Medicine.

Eligibility criteria

Patients had to present with previously untreated histologically confirmed mesothelioma . An assessable or measurable lesion has to be present. Patients should not have prior history of malignancy or previous chemotherapy intake . Other eligibility criteria included Karnofsky performance status ≥60, good renal function (serum creatinine level≤1.5 mg/dl and creatinine clearance ≥ 90 ml/min), hepatic function (serum bilirubin level≤1.1 mg/dl , aspartate and alanine transferase levels up to 3 times the upper limit of normal) and haematological profile (neutrophil count ≥2000 mm–3 , hemoglobin > 9 g/dL and platelet count ≥100,000 mm–3) .

Exclusion criteria

Patients presenting with recent (<3 months before the date of treatment) myocardial infarction, congestive heart failure or cardiac arrhythmia requiring medical treatment, uncontrolled infectious disease or other serious medical or psychiatric illness precluding adherence to the study protocol were excluded.

Investigations

Initial work-up included clinical evaluation completed by weight, height, surface area and record of Karnofsky performance status, complete blood sampling including evaluation of creatinine clearance , chest X-ray and CT scan (in case of pleurodesis, chest CT scan must be repeated before administration of the first course of chemotherapy), abdominal ultrasound, isotopic or echographic left ventricular assessment and assessment of hearing by audiometry .

Blood sampling were performed before each cycle . An evaluation after each three courses of chemotherapy was performed with the same tests as during the initial work-up . This assessment was repeated every three cycles. After treatment completion, patients were followed every 2 months with clinical evaluation. Chest X-ray and biological tests if needed .

Treatment

The chemotherapy regimen consisted in the combination of cisplatin and adriamycine. Adriamycine (50mg/m2) was given as a 30 min intravenous infusion over 2 days (D1-2) , just before cisplatin administration. Cisplatin (80mg/m2) was administered over 120 min in 500 ml NaCl 0.9%, after pre-hydration with 1.5 liters of 0.9% NaCl for 6 h and followed by a mannitol-induced diuresis over 3 days (D1-3). The recommended antiemetic regimen was a combination of dexamethasone and granisetron or zofran .

Courses were repeated every 3—4 weeks, as soon as haematological (neutrophils > 1500 mm–3 , hemoglobin > 9 g/dL and platelets > 100,000 mm–3) and renal (creatinine < 1.1 mg/dl and creatinine clearance ≥ 90 ml/min) functions have recovered.

The patient went off treatment if myelosuppression persisted on day 36 , progressive impairment of cardiac function as evaluated by left ventricular assessment or hearing function as evaluated by audiometry .

Criteria of evaluation

Patients were considered assessable if three courses of chemotherapy were completed. Patients with early progression or death prior to evaluation due to malignant disease or toxicity and treatment cessation due to toxicity were considered as treatment failures and incorporated in the evaluable patients.

Duration of response was calculated from the day of registration until the date of first observation of progressive disease. Survival was dated from the day of registration.

Response was evaluated by a complete restaging after each three courses. Complete remission was defined as the disappearance of all signs of disease. Partial response was defined as a 50% or greater decrease in the lesions for at least 3 weeks in the absence of progressive disease or occurrence of new lesions elsewhere. Progression was considered to be an increase of greater than 25% in lesion or the appearance of a new lesion, irrespective of response elsewhere. All other circumstances were classified as no change. WHO criteria were used to assess toxicity.

Statistical methods

Kaplan Meier method was used for estimating overall survival, and relapse free survival. P-value is considered significant at 0.05 level. Numerical data were described in terms of means and medians for central tendency and standard deviation and range, minimum and maximum for dispersion.

Results

Between December 2005 and March 2007 , 30 patients were registered . Five patients were deemed ineligible due to poor performance status and were offered supportive treatment only .

Characteristics of 25 eligible patients are shown in table 1 . The majority of patients were males (60%) , had a good performance status of 70 or more on Karnofsky scale (72%) and presented with epithelial histology subtype (68%) . Most of the patients had assessable disease (84%) and most of them presented with platelet count ≤ 400.000 /μL (88%) .

Table 1: Characteristics of 25 eligible patients with malignant mesothelioma

Eligible	25
Gender	
Male	16
Female	9

Median age (range)	48 (28-65)
Performance status	
60	7
70	15
80	3
Histology	
Epithelial	17
Sarcomatoid	5
Biphasic	3
Disease assessment	
Measurable	4
Assessable	21
Platelet count (/μL)	
> 350.000	3
≤ 350.000	22

Overall 111 chemotherapy cycles were administrated along the study, ranging from one to six per patient. Fourteen patients completed six cycles, eight patients received three cycles and three patients received one cycle of chemotherapy cisplatin and adriamycine. After one cycle three patients had disease progression and after three cycles eight more patients had disease progression and shifted to another line of treatment. After six cycles of treatment four patients had partial response and ten patient had stable disease.

Overall response rate was 16%. Stabilization rate including partial response and no change was 56%. Median response duration was 8 months (range 4 – 12 months). Median overall survival was 12 months (range 7 – 16 months).

Table 2: Response frequencies

Response	No	%
Complete	0	0
Partial	4	16%
Stable	10	40%
Progression	11	44%

As expected, the main toxicities were nausea and vomiting, neutropenia, thrombocytopenia and alopecia. No toxic death was documented. Highest toxicity per patient during the whole course of treatment is reported in table 3 .

Table 3: Highest toxicity during the whole treatment among patients at least receiving three cycles of chemotherapy (n=25)

	0	I	II	III	IV
Neutropenia	1	8	8	6	2
Thrombocytopenia	9	4	7	4	1
Nausea	2	8	9	6	-
Diarrhea	20	2	3	-	-
Stomatitis	14	2	5	4	-
Infection	20	2	3	-	-
Neurologic	19	2	4	-	-
Cardiac	25	-	-	-	-
Hearing loss	-	14	11	-	-
Nephrotoxicity	13	5	7	-	-

A prognostic factors analysis for survival was performed . In univariate analysis, age (p = 0.71) , gender (p = 0.61) , histology (epithelial versus other ; p = 0.08)) , and platelet count (p = 0.06) were not considered as significant factors. Performance status (p = 0.04) was considered as potential prognostic factor for overall survival.

Discussion

The reasons for a lack of consensus in the management of mesothelioma are partly historical, partly related to the unique biology of the tumor and partly due to failure so far to find any single treatment or treatment combination which offers more than short-term tumor suppression in most patients. Historically, the very existence of a primary tumor of the pleura was disputed in the first half of this century (12) and, even when it became accepted as a distinct entity with a clear relationship to asbestos exposure in many patients (13), difficulties were still encountered in distinguishing the tumor from adenocarcinoma in many instances (14).

Until more sophisticated immunocytochemical techniques were developed to distinguish between epithelial mesothelioma an adenocarcinoma, there is no doubt that many cases treated as mesothelioma were, in fact, cases of secondary adenocarcinoma. This added to the confusion in the interpretation of the results of treatment (15).

The biological behavior of mesothelioma is distinct from that of other solid tumors in that mesothelioma tends to grow in a sheet-like fashion, covering the surface of the parietal and then the visceral pleura; it shows little tendency to invade structures deep into the pleura in the early course of the disease, unless the pleura is breached by needles or tubes, when it will spread readily along needle or tube tracks (16).

Part of the explanation for this unusual behavior appears to lie in the relative lack of proteases in comparison to other solid tumors (17). In many instances the tumor appears to begin in a multifocal fashion resulting in scattered deposits of tumor with normal pleura intervening, suggesting either that a field change has occurred throughout the pleura, or that the tumor has metastasized locally within the pleural cavity (18).

Because the tumor is either broadly extensive on the pleural surface or multifocal at the time of detection, it does not lend itself to localized surgical excision. Surgical treatment aimed at complete resection therefore has to be much more extensive and is only suitable for a minority of patients (15) .

Currently, the treatment of malignant mesothelioma remains controversial. No single therapy has demonstrated to have an impact on survival in randomized trials. In a randomized feasibility study, chemotherapy allowed a better symptom control than best supportive care alone (11).

However, malignant mesothelioma is considered by most oncology physicians as a poorly chemotherapy sensitive tumor and there is no universally accepted standard chemotherapy. In a previous review (7), it was found that cisplatin plus doxorubicin was one of the most active chemotherapy regimens with an overall RR of 28.5% (9) .

In the study , cisplatin and adriamycine was associated with overall response rate was 16% , stabilization rate including partial response and no change was 56% and median response duration was 8 months (range 4 – 12 months) with median survival of 12 months (range 7 – 16 months) that is comparable to other

chemotherapy regimens used to treat pleural mesothelioma (3 , 4 , 5 and 9) . Low response rate and short duration of median survival can be attributed to small sample size and short duration of follow up due to non coherence of patients on follow up schedules due to some financial and social factors .

The toxicity profile is comparable to the study done by Berghmans et al . 2005 (9) using cisplatin and epirubicin combination. The main toxicities were nausea and vomiting , neutropenia , thrombocytopenia and alopecia . No sever renal toxicity was noted that necessitate discontinue of treatment and also no persistent hearing was noted . No gross cardiac toxicity was noted.

The prognostic role of multiple factors on survival has been investigated in malignant mesothelioma in numerous studies. Stage, performance status, histology and WBC count were commonly reported as having a significant impact on survival. In the study, only performance status was noted as a potential prognostic factor for overall survival mostly due to low sample size,

In 1998, the European Organization for Research and Treatment of Cancer (EORTC) identified several prognostic variables for the course of the disease. In a multivariate analysis of the EORTC, poor prognosis was associated with high WBC count , poor performance status, low hemoglobin level, probable/ possible histologic diagnosis of mesothelioma and having sarcomatous histologic subtype (19).

Likewise, the Cancer and Leukemia Group B (CALGB) analyzed several pretreatment factors pooled from seven phase II studies that were predictive of poor survival and defined six prognostic groups. Poor prognosis was seen in patients with the following criteria: age older than 75 years, poor performance status, chest pain, dyspnoea, weight loss, high white blood cell count, elevated platelet count, low haemoglobin, elevated serum lactate dehydrogenase levels, pleural effusion and nonepithelial histology (20).

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