

## Docetaxel plus Gemcitabine as First-line Treatment in Malignant Pleural Mesothelioma: A Single Institution Phase II Study

MARIA RALLI, IOANNIS TOURKANTONIS, NEKTARIA MAKRILIA, ELENI GKINI, ELIAS KOTTEAS, IOANNIS GKIOZOS, NIKOLAOS KATIRTZOGLU and KOSTAS SYRIGOS

*Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Athens, Greece*

**Abstract.** *Background: The cisplatin-pemetrexed and cisplatin-gemcitabine combinations are considered the standard treatment for malignant pleural mesothelioma. The purpose of this study was to examine the efficacy of gemcitabine plus docetaxel in the first-line setting, as this combination has not been investigated in mesothelioma before. Patients and Methods: Twenty-five consecutive patients with malignant pleural mesothelioma were enrolled. They received 80 mg/m<sup>2</sup> of docetaxel and 1,000 mg/m<sup>2</sup> of gemcitabine on days 1 and 14 of a 28-day cycle. The treatment was scheduled for a maximum of 6 cycles or until disease progression or unacceptable toxicity. Results: A total of 7 out of our 25 patients (28%) responded to treatment. In 14 patients (56%), the disease remained stable, while in 4 (16%) it progressed. The median time to progression was 7 months (range: 5.4-8.6 months) and the median overall survival was 15 months (range: 12.4-17.5 months). Conclusion: The administration of gemcitabine and doctaxel appears to be promising first-line therapy for patients with mesothelioma, as it is well tolerated and appears to improve survival.*

Malignant pleural mesothelioma (MPM) is a rare aggressive tumor caused mainly by occupational asbestos exposure. Its incidence reaches 100 cases/million/year in occupationally exposed populations as opposed to 1 case/million/year in the general population and data show that it will continue to increase until 2020-2030 (1).

*Correspondence to:* Maria Ralli, MD, Oncology Unit, 3rd Department of Medicine, Athens University School of Medicine, Building Z, Sotiria General Hospital, Mesogion 152, 115 27 Athens, Greece. Tel: +30 2107475034, Fax: +30 2107781035, e-mail: rallh79@yahoo.gr

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The rarity of MPM and its often subtle clinical manifestation may lead to a missed or delayed diagnosis. The current treatment of advanced malignant pleural mesothelioma is platinum-based combination chemotherapy (2, 3). The landmark trial that compared the combination of cisplatin plus pemetrexed to cisplatin monotherapy demonstrated a survival benefit of 2.8 months for the combination arm (4). A subsequent trial showed a 2.6 month improvement in the survival of patients who were treated with cisplatin plus raltitrexed when compared to the survival of those who received cisplatin alone (5). Response rates for the combination treatments were 41.3% and 23.6%, while median overall survival time was 12.1 and 11.4 months respectively (6). The combination of cisplatin and gemcitabine has demonstrated comparable response and survival rates in several phase II trials (7-10), although it has not yet been evaluated in any randomized clinical trial.

A phase II trial examining the effectiveness of docetaxel in patients with MPM had been launched but was terminated early, after the first accrual stage, because of an insufficient number of patients with complete or partial disease response. There is no evidence of docetaxel being an effective agent as monotherapy in malignant mesothelioma (11). The efficacy of gemcitabine as a single-agent against mesothelioma is also limited when used in clinical practice (12). Bi-weekly administration of a docetaxel/gemcitabine combination constitutes a tolerable and convenient regimen for the treatment of advanced non-small cell lung cancer, with efficacy similar to most standard-platinum based therapy (13-15) but there have been no clinical trials investigating this combination in MPM therapy. We therefore conducted a preliminary phase II trial to evaluate the anti tumor efficacy of this double treatment, as determined by objective response, time to progression, overall survival and quality of life.

### Patients and Methods

Twenty-five patients with measurable, histologically confirmed MPM were enrolled in the present study. Patients were older than 18 years of age and had an Eastern Cooperative Oncology group performance status of 0-1. They had no uncontrolled cardiac or

hepatic disease. Adequate bone marrow function (total leukocyte count  $\geq 3000 \mu\text{l}^{-1}$ , absolute neutrophil count  $\geq 1,500 \mu\text{l}^{-1}$ ), hepatic function (bilirubin  $\leq 2 \text{ mg/dl}$ , aspartate aminotransferase and alanine aminotransferase  $\leq 2.5$  times the institutional upper limit of normal) and renal function (estimated creatinine clearance  $\geq 60 \text{ ml/min}$  and serum creatinine  $\leq$  twice the institutional upper limit of normal) were required. Patients with prior malignancies (other than non-melanoma skin cancer and adequately treated cervical cancer) were excluded if the disease-free interval from the other malignancy was less than 5 years. Pregnant or nursing mothers were also excluded. Patients with reproductive potential were required to use an effective contraceptive method. None of the patients had received chemotherapy before recruitment. Prophylactic superficial irradiation of the chest drain or biopsy scars was allowed before commencement of chemotherapy; provided the patients had recovered from all side-effects associated with the procedures and that they had measurable disease outside the irradiated site.

The study was approved by each individual Institutional Review Board, and written informed consent was obtained from each patient in accordance with institutional and government guidelines.

**Treatment plan.** A complete medical history was obtained at baseline. Data regarding cellular differentiation, previous radiotherapy or surgery, disease location, pericardium or peritoneum involvement and weight loss by the time of diagnosis were also recorded. Gemcitabine was administered at a dose of  $1,000 \text{ mg/m}^2$  diluted in 500 ml 5% dextrose and was followed by docetaxel  $80 \text{ mg/m}^2$  diluted in 500 ml 5% dextrose. Treatment was administered on an out patient basis on day 1 and 14 of 28-day cycles. In the absence of disease progression and unacceptable toxicity, treatment was continued for a maximum of 6 cycles.

**Assessment of response.** After the 3rd and 6th cycle of chemotherapy, patient response was assessed by computed tomography (CT) scans. The best way of assessing treatment response in MPM is still under debate. In our study, we used the latest guidelines to evaluate the response to treatment in solid tumors (Response Evaluation Criteria in Solid Tumours, RECIST) (16). If separate mass lesions were not identifiable, then the thickness of the circumferential pleural tumour was measured on three separate levels on transverse sections (17)]. In each CT scan, the sum of the largest measurements was obtained and compared to that of the baseline scan.

Duration of response was defined as the interval from the time that the criteria for partial response (PR) were first met to the time that criteria for disease progression (PD) were first met, taking the smallest sum of largest diameters (since treatment started) as reference. Duration of stable disease (SD) was defined as the interval from the start of treatment to the time that criteria for progressive disease were first met, taking the smallest sum of largest diameters (since treatment started) as reference.

**Statistical analysis.** Overall survival (OS), overall response rate (ORR) and time to progression (TTP) were assessed in all enrolled patients on an intention-to-treat basis. The duration of response was calculated from the day of the first documented response until disease progression. TTP was defined as the time from study entry (first day of study treatment) until disease progression (as shown by radiological or clinical examination) or death by any cause. Patients without any evidence of progressive disease were censored at the date

Table I. Patient demographics and baseline characteristics.

	n (%)
Gender	
Male	21/25 (84%)
Female	4/25 (16%)
Age (years)	
Median	66
Range	44-78
Smoking exposure	
Yes	24/25 (96%)
No	1/25 (4%)
Histopathology	
Epithelioid	19/25 (76%)
Sarcomatoid	6/25 (24%)
Performance status	
0	10/25 (40%)
1	15/25 (60%)
Asbestos exposure	
Yes	12/25 (48%)
No	13/25 (52%)
Bone metastases	
Yes	10/25 (40%)
No	15/25 (60%)
Stage at the time of diagnosis	
I	4/25 (16%)
II	7/25 (28%)
III	6/25 (24%)
IV	8/25 (32%)

of the last follow-up. OS was calculated as the time from study entry until death by any cause. Patients who were alive on the date of last follow-up were censored on that date. For time events, the actuarial survival function was estimated by the Kaplan-Meier method.

## Results

Patients' baseline characteristics are shown in Table I. The response rate was evaluated in all 25 patients. The disease showed PR in 7 patients (28%), remained stable in 14 patients (56%), whereas it progressed in 4 patients (16%). The percentage of patients who achieved SD or PR reached 84% (21 out of 25 patients). The median TTP was 8 months (Figure 1a), with median OS of 15 months (Figure 1b). Univariate subgroup analysis showed that gender, age, stage and time to treatment from diagnosis did not affect survival rates.

## Discussion

Chemotherapy in MPM continues to be a challenge. Short overall survival and a limited number of cases (as compared to other chest tumors) represent some of the obstacles to be overcome. The pemetrexed plus cisplatin combination is considered the benchmark front-line regimen for this disease, based on a phase III trial in 456 patients that yielded a response

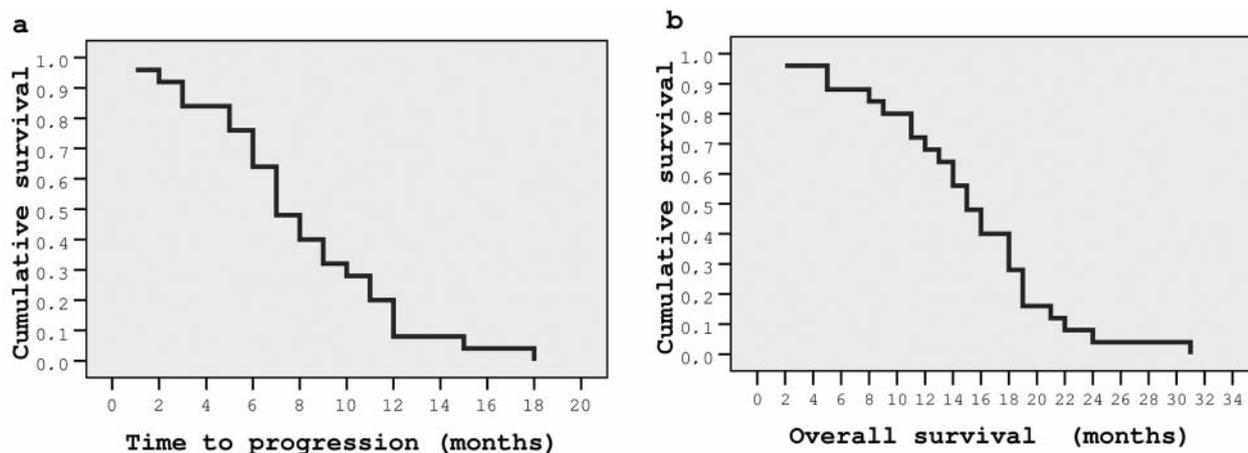


Figure 1. Statistical analysis (Kaplan-Meier curves) of time to progression and overall survival. a, Median time to progression was 8 months; b, median overall survival was 15 months.

rate of 41% and a median survival of 12.1 months(18). Other combination regimens have also been reported and show higher response rates in small phase II trials. Among the combination regimens, the one that includes doxorubicin and cisplatin has been the most widely used in phase II studies (19-20). Recently, oxaliplatin-containing combinations have shown results in phase II studies: the overall survival was 20% in the oxaliplatin-raltitrexed combination (21), 23% in the oxaliplatin-vinorelbine combination (22) and 40% in the oxaliplatin-gemcitabine combination (23). One large phase III randomized trial compared the cisplatin plus pemetrexed combination (226 patients) to cisplatin monotherapy (222 patients) and demonstrated a significant advantage in OS (41.3% vs. 16.7%), in TTP (5.7 months vs. 3.9 months) as well as in median and OS (12.1 months vs. 9.3 months) in the combination arm (4). Another phase III clinical trial compared the cisplatin plus raltitrexed combination (126 patients) to cisplatin alone (124 patients): overall survival was 24% vs. 14%, respectively (5).

Vascular endothelial growth factor (VEGF) appears to be an important autocrine growth factor for malignant mesothelioma, with high serum VEGF levels being a negative prognostic factor in these patients (24). Bevacizumab is a recombinant humanized monoclonal antibody to VEGF, which blocks angiogenesis by neutralization of VEGF. A phase II study with cisplatin and gemcitabine with bevacizumab is ongoing (25).

In the present study, we evaluated the impact of gemcitabine plus docetaxel in patients with MPM and it should be noted that this is the first time that this non-platinum combination has been evaluated in MPM therapy. Our results appear to be very encouraging since the overall survival was 15 months. Given the progress made in recent years, there is reason to believe that more effective treatments will continue to be developed.

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