Abstract. Malignant pleural mesothelioma (MPM) is an aggressive treatment-resistant tumor with a median survival from diagnosis of 12 months. Although multimodality protocols that combine aggressive surgery and adjuvant chemotherapy or radiotherapy have shown improved survival in selected cases, the majority of patients with MPM are not suitable for radical surgery due to advanced stage and comorbid medical illness. For these patients combination chemotherapy with Pemetrex and Cisplatin should be considered for first line palliative chemotherapy. The therapeutic options available to patients with MPM resistant or refractory to systemic chemotherapy are very limited. Thoracic "stop-flow" perfusion (TSP) is a semi-invasive loco-regional drug delivery system that, limiting the circulation to the thorax during the anticancer agent's infusion, claims the advantage of reaching high drug concentration at the tumor site while maintaining a low systemic toxicity. The aim of this phase I-II study was to evaluate the toxicity profile and efficacy of two different platinum-based combined regimens – cisplatin plus mitomycin-C (MMC) and cisplatin plus melphalan (L-PAM) – administered using TSP technique in patients with advanced or recurrent MPM who had refractory disease after systemic first line chemotherapy. Patients with histologically proven unresectable stage II-III MPM entered this trial. Between January 1995 and December 2001, 27 patients were enrolled in the study and submitted to TSP using the two different chemotherapy cisplatin based regimens: 12 patients received cisplatin 100 mg/m² plus MMC 20 mg/m² (MMC arm) and 15 cisplatin 100 mg/m² plus L-PAM 50 mg/m² (L-PAM arm). Objective responses were assessed by CT-scan 30 and 60 days after the end of treatment in all 27 enrolled patients. Two patients (7.4%) achieved a complete response, 2 (7.4%) a partial response and 4 (14.8%) a minor response. The remaining 19 patients (70.3%) showed a stable disease. No patients developed progression of the disease following the first TSP. The overall median time to progression was 8.9 months (range 1-41). The median survival time for all patients from the beginning of regional chemotherapy was 16.6 months, with a 1-year survival rate of 62.9%, a 2-year survival rate of 18.5%, and a 3-year survival rate of 7.4%. Our data show that TSP is a relatively effective second-line treatment in patients with progressive disease after systemic chemotherapy, with a low rate of major complications and treatment-related toxicity.

Malignant pleural mesothelioma (MPM) is a locally aggressive and often fatal malignancy (1). The median survival of patients with MPM from the time of diagnosis is approximately 12 months (2). There is no effective therapy for MPM. In the past, single modality options using surgery, radiotherapy or chemotherapy have not demonstrated a survival benefit (3). Multimodality protocols that combined surgery, with debulking or radical intent, with chemotherapy or radiotherapy have been proposed, but improvement on overall survival has been obtained in only a highly selected group of patients (i.e., epithelial histology, no nodal involvement and clear resection margins) submitted to extrapleural pneumectomy (EPP) (4, 5). However, at the moment of diagnosis, more than 50% of the patients were not suitable for EPP due to advanced stage or other concurrent illness. For these patients surgery may be required to establish the diagnosis, to perform a cytoreduction and to palliate the symptoms.

Recently, combination chemotherapy with Pemetrex and Cisplatin has shown improvement in both survival and symptomatic relief in patients with unresectable MPM and, to date, it has been considered as standard for first line palliative chemotherapy (6). Unfortunately, the therapeutic options available for patients with MPM resistant or refractory to systemic chemotherapy are very limited. There...
is no second-line chemotherapy regimen that could be described as standard. In the search for new therapeutic options, loco-regional chemotherapy claims the advantage of delivering higher drug concentrations to the target region than safely possible with systemic administration. This objective can be reached in the thoracic region by intrapleural antineoplastic drug instillation or by a semi-invasive technique called thoracic stop flow perfusion (TSP). TSP limits the circulation to the thorax during the chemotherapy infusion by placing balloon catheters in the aorta and vena cava and Esmarch’s bandage around the roots of both arms.

At the Department of General Surgery of the University of L’Aquila, regional chemotherapy performed by the "stop flow" technique has been used since 1993 to treat advanced thoracic, abdominal or pelvic malignancies. During these years, the "stop flow" perfusion has been shown to be safe with only transient hemodynamic and oxygenation changes (7).

The aim of this phase I-II study was to evaluate the toxicity profile and efficacy of two different platinum-based combined regimens – cisplatin plus mitomycin-C (MMC) and cisplatin plus melphalan (L-PAM) – administered using the TSP technique in patients with advanced or recurrent MPM who have refractory disease after systemic first line chemotherapy.

Patients and Methods

Patient selection. Patients with histologically proven unresectable stage II-III MPM entered this trial, provided that they had received systemic first-line chemotherapy and one treatment previously, such as radiotherapy or surgery. Eligibility criteria were: uni- or bidimensional measurable disease, age >18 years, acceptable performance status [≤3 according to the Eastern Cooperative Oncology Grade (ECOG)], an estimated life expectancy of >3 months, adequate bone marrow reserve and hepatic and renal function. Patients were eligible 6 weeks after previous treatment. Written consent was obtained from all patients after they had been given complete information about the disease and the implication of the proposed experimental palliative treatment.

Study design. This phase I-II evaluation trial was an uncontrolled study comparing two different platinum based chemotherapy regimens MMC versus L-PAM) administered during TSP via a central venous line.

The response rate, duration of tumor response and time-to-progression of the disease were the primary end-points of the study. The overall survival was the second end-point.

Study flow. Patient recruitment started in January 1995. By December 2001, 34 patients had been enrolled. Seven patients did not meet the eligibility criteria (incorrect staging four cases, absence of adequate performance status or bone marrow reserve three cases) and 27 patients were eligible and assessable. At the present time all enrolled patients have died.

Treatment plan. The treatment plan consisted of two different platinum-based combined chemotherapy regimens administered during TSP via central venous line: cisplatin 100 mg/m² plus MMC 20 mg/m² and cisplatin 100 mg/m² plus L-PAM 50 mg/m². The perfusion was repeated when 30-40 days after the first treatment the eligibility criteria were still present. In case of leucocytopenia or thrombocytopenia (WHO grade 3 or 4), the next therapy cycle was postponed until the white blood cell count was >3,000/dl and platelet count >100,000/dl. Granulocyte stimulating factors (G-CSF) were used when necessary. Treatment was discontinued, if disease progression or major toxicity occurred, or if the patient or physician decided that this was appropriate.

Toxicity and response. Therapy-induced toxicity was graded according to WHO criteria (8) after each therapy course.

The definition of response, as assessed by CT-scan 30 days after the end of treatment, was based on standardized response criteria (9). Partial or minor responses were confirmed by a second CT-scan four weeks later. The duration of tumor response was defined as the time from first objective status of response to the time of documented disease progression. Survival was defined as the time from the first TSP to the time of death from any cause.

Operative technique. Details about the TSP technique, anesthesia management and hemofiltration criteria have been previously reported (7, 10). Figure 1 shows a schematic representation of TSP.

Results

Twelve patients received cisplatin plus MMC (MMC arm) and 15 cisplatin and L-PAM (L-PAM arm). All the patients were male with a median age of 51.1 (range 38-65). Most patients had epithelioid histology (75%), stage III (70.3%) and ECOG performance status 2 (70.3%). All patients had prior palliative surgery and systemic chemotherapy.

Mesothelioma related symptoms were documented in 23 patients at the beginning of treatment: dyspnoea (60.8%), chest pain (43.5%) and cough (4.3%). One patient had monolateral malignant pleural effusion.

Tumor response and time-to-event outcomes. Objective responses were assessed by CT-scan 30 days and confirmed 60 days after the end of treatment in all 27 enrolled patients. Two patients (7.4%) achieved a complete response (CR), two (7.4%) a partial response (PR) and four (14.8%) a minor response (MR). The remaining 19 patients (70.3%) showed a stable disease (SD). No patients developed progression of the disease following the treatment. Among the 15 patients treated with cisplatin and L-PAM (L-PAM arm), two patients (13.3%) experienced a CR, one patient (6.6%) a PR, two patients (13.3%) a MR and ten patients (66.6%) a SD.

No patients treated with cisplatin plus MMC had a CR but PR and MR were recorded in 1 (8.3%) and two (16.6%) patients, respectively. The remaining nine patients (75%) had a SD.

The overall median time to progression was 8.9 months (range 1-41). The median time to progression was 9.2 months (range 3-20) in L-PAM arm and 8.5 months (range 1-41) in MMC arm. No patients received systemic chemotherapy, radiotherapy or surgery after the infusion treatment.
The median survival time for all patients from the start of regional chemotherapy was 16.6 months, with a 1-year survival rate of 62.9%, a 2-year survival rate of 18.5% and a 3-year survival rate of 7.4%. The overall survival curves for all enrolled patients and for stage II and III are shown in Figure 2.

**Procedure related complications.** Sixty treatment cycles (TPS and hemofiltration) were administered to 27 patients (range 1-7). All patients survived the procedures. No perfusion had to be terminated early due to the severe hemodynamic and oxygenation changes. No technical complications during the procedure were recorded.

**Hypoxic abdominal perfusion related toxicity.** Toxicity was evaluated for all subjects over the sixty procedures. Four cases (14.8%) of severe hematological toxicity (WHO grade 3-4) were recorded: two cases of thrombocytopenia and two cases of leukopenia. All the cases of grade III-IV hematological toxicity were induced by the first TSP. There was no occurrence of hemorrhage due to the lack of platelets. G-CSF were used when necessary (leukopenia >2,000 µl) but no infectious episodes were recorded during the phase of leukopenia.

There were no cases of severe non-hematological (WHO grade 3-4) adverse events in this study. Four patients (14.8%) developed mild non-hematological toxicity (WHO grade 1-2): there were three cases of vomiting and diarrhea and one case of acute cystitis. No treatment-related deaths occurred.

**Discussion**

MPM shows a poor response to standard systemic chemotherapy. Until a few years ago, single or combination chemotherapy regimens have shown a response rate of 20% or less and no survival advantage has ever been clearly demonstrated (6). These results have not supported the routine use of chemotherapy in the MPM treatment. Recently, newer agents seemed to be more effective. In a large phase III study the use of pemetrexed plus cisplatin in patients with unresectable MPM was associated with significantly improved survival time and overall greater antitumor activity compared to cisplatin alone (11). This trial established pemetrexed and cisplatin as a new standard in systemic therapy of unresectable MPM (6).
Patients with recurrent MPM after first-line systemic chemotherapy are managed by supportive care alone due to the rapid worsening of their general condition that contraindicates further treatment. However, despite there being no evidence that second-line chemotherapy can influence survival in these cases, there is some suggestion that second-line treatment may be appropriate for patients with good performance status who experience disease progression after systemic chemotherapy. Few data are available about second-line chemotherapy because the majority of MPM chemotherapy trials have included only chemotherapy-naïve patients. However, several phase II trials have evaluated the effectiveness of chemotherapy in previously treated patients. Giaccone et al., using ZD0473, a platinum analogue, reported 12% with a minor response, 40% with stable disease, but no complete or partial responses were seen in this trial; the median time to progression and death was 77 days (12). Fizazi et al., in a phase II study, treated chemotherapy-naïve patients and pretreated patients using raltitrexed and oxaliplatin; the partial response rate was 20% for both patient groups with a median survival in pretreated patients of 44 weeks from the start of the treatment (13). This encouraging result was not confirmed by Porta et al. who studied the antitumor activity of the same combination chemotherapy as a second-line treatment of MPM; the trial was closed because chemotherapy, though well-tolerated, yielded no objective response with a median survival of just 14 weeks (14).

In our series 30% of the patients experienced tumor response to treatment with a median time-to-progression of 8.9 months and median survival time, from the start of regional chemotherapy, of 16.6 months. Compared to the other second-line treatment studies, our response and survival rates were very encouraging. The treatment was well-tolerated by the patients and a low rate of serious systemic toxicity was encountered: these data might be explained by the routine use of hemofiltration of the perfusate at the end of the procedure. MPM tends to remain confined to the hemithorax, and is mainly characterized by locoregional growth and spread. The failure to achieve disease control in the thorax remains the primary problem in treating this tumor. In our trial, local control of the disease was obtained in more than 70% of the treated patients and majority of the patients died due to extrathoracic progression of the disease. This result seems to support the hypothesis that TSP is a technique which increases local drug concentrations enough to break through tumor cell resistance in MPM, improving local control of the tumor and survival rate of patients refractory to systemic chemotherapy.

References


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