

Phase II study of melphalan as a single-agent infused over a 24-hour period with individual adapted dosing in patients with recurrent epithelial ovarian cancer

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Abstract. The current study was performed to evaluate the efficacy and toxicity of a chemotherapy treatment using melphalan administered over a 24-h period with individual adapted dosing in advanced ovarian cancer. Melphalan was infused intravenously with an automatic infusion pump over a 24-h period. The schedule was repeated every 28 days for a maximum of 6 cycles. The initial administered dose was 25 mg/m². Drug adjustment was then made using a population approach, with the aim of constraining the overall area under the plasma concentration-time curve within 2.0-2.5 mg · h/l. A total of 96 courses of chemotherapy was administered. The toxicity profile did not differ greatly from that reported after a 1-h infusion and was acceptable in such a heavily pretreated patient population. Twenty-five patients were assessable for response and survival. Four (16%) partial responses were observed, which lasted 9, 10, 13 and 37 months, respectively. Three patients experienced stable disease during 8, 14 and 22 months, respectively. The 1- and 2-year survival rates were 18% and 6%, respectively. At the time of analysis, two patients remained alive with progressive disease at 22 and 37 months, respectively. In conclusion, melphalan administered over a 24-h period in platinum- and taxane-resistant ovarian cancer patients appeared to provide some clinical benefits with manageable toxicity. Based on these results, future studies comparing melphalan administered over a 24-h period and oral melphalan administrations will be scheduled.

Introduction

Advanced ovarian cancer remains the most lethal of all gynecological neoplasias (1). About 75% of women diagnosed

with epithelial ovarian cancer present when the disease is already at an advanced stage (FIGO stage III or IV) (2). Extensive surgical resection followed by platinum-based combination chemotherapy results in a high rate of initial response. Indeed, the combination of cisplatin or carboplatin with paclitaxel has become the reference first-line chemotherapy treatment (3-6). However, a distressingly high percentage of those women with a complete response will experience relapse. Although there are many active agents for treating women with relapsed ovarian cancer, there is no predictably curative therapy, especially for those with multisite relapse.

Melphalan entered clinical use in the late 1950s and has since established itself as an agent with a wide spectrum of antitumor activity including ovarian cancer (7-11). Melphalan is an alkylating agent of the bischloroethylamine type that affects cytotoxicity by forming either interstrand, intrastrand, or DNA-protein cross links (8). After a short intravenous infusion, melphalan rapidly disappears from the plasma. Preclinical studies suggested that prolonged infusion of melphalan might be more active than short infusion (12,13). Moreover, based on pharmacokinetic considerations (short half-life, small volume of distribution and low protein binding capacity), melphalan is a good candidate for continuous infusion. However, due to its low stability either in 5.0% dextrose or 0.9% sodium chloride, melphalan is usually administered by short-term infusion. In this setting, we have previously shown that the stability of melphalan can be increased using 3.0% sodium chloride (14), and the maximum tolerated dose of melphalan infused over a 24-h period was 30 mg/m² in a phase I trial (15).

In the present study, we report on the results of a phase II study initiated to determine the efficacy and toxicity of a chemotherapy treatment using melphalan administered over a 24-h period with individual adapted dosing in advanced ovarian cancer.

Patients and methods

Patients and eligibility criteria. The study protocol was reviewed and approved by the Board for the Protection of Persons subjected to Biomedical Research of Montpellier.

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Table I. Patient characteristics.

Characteristics	Mean (range)	No. of patients
Total no. of patients		33
Age (years)	60 (40-82)	
Weight (kg)	60 (38-80)	
WHO performance status		
0		5
1		13
2		15
FIGO stage at diagnosis		
I		2
II		1
III		23
IV		7
Histological type		
Serous		20
Other		13
Involved sites		
Peritoneum		24
Lymph nodes		5
Lung		2
Liver		6
Brain		2
Pleura		3
Bone		1
Others		8
Radiotherapy		1
Surgery		33
Line of chemotherapy		
Second-line		7
Third-line		21
Fourth-line		5
Previous chemotherapy		
Platin salts/taxanes		28
Cyclophosphamide/platin salts		12
Paclitaxel by intraperitoneal route		4
Others		18
Serum CA125 levels (IU/ml)		
>ULN to ≤10x ULN		7
>10x ULN to ≤100x ULN		15
>100x ULN		4
ULN, upper limit of normal.		

Table II. Courses of chemotherapy.

No. of courses	No. of patients
1	6
2	14
3	3
4	3
5	1
6	6

consent to participate in the trial, after reading an information leaflet and having the opportunity to ask questions relating to the trial.

Female patients entering this phase II study were required to have histologically proven metastatic epithelial ovarian carcinoma. Patients were required to have received at least one prior platinum-based regimen, and no more than three prior chemotherapy regimens, which could be taxane-based. Complete history, physical examination, chemistry panel, complete blood count, platelet count and evaluation of extent of tumour (using appropriate investigations) were required prior to the study entry. Patients had at least a ≥4-week interval between their last chemotherapy regimen and the start of study treatment. Eligibility criteria for the study included the following: 1) 18 years of age or older; 2) a performance status of 0-2 on the Eastern Cooperative Oncology Group (ECOG) scale; 3) bidimensionally measurable disease; 4) adequate bone marrow [white blood cells (WBC) count ≥4,000/mm³, polynuclear neutrophils ≥1,500/mm³ and platelet count ≥100,000/mm³]; 5) liver [alanine transferase (ALT)/aspartate transferase (AST) ≤2x the upper limit of normal (ULN) or ≤3x ULN in cases of liver metastasis, total bilirubin ≤1.25x ULN] and renal (creatinine ≤2x ULN and creatinine clearance >50 ml/min) functions; and 6) cardiac ejection fraction >50% by echocardiographic or radionuclide cineangiography.

Pretreatment evaluation and follow-up. Evaluation prior to treatment consisted of detailed clinical history and physical examination, full blood counts with differential white cell count and platelets, blood chemistry including electrolytes, albumin, renal and hepatic function tests, serum tumor markers (CA125), and computed tomography scan of the thorax, abdomen and pelvis.

During the treatment period, patients were required to undergo the following procedure: weekly assessment of toxicity and blood counts; blood chemistry on the first day of each course of chemotherapy including electrolytes, creatinine, total protein, albumin, calcium, glucose, alkaline phosphatase, total and direct bilirubin, AST and ALT); physical examination before each course.

Treatment regimen. Melphalan was infused intravenously by an automatic infusion pump over a 24-h period, which was started at 8 p.m. The drug was dissolved in 4 syringes of 60 ml 3% sodium chloride, with each syringe administered intravenously over 6 h through a central venous catheter. Before administration, syringes were stored at 4°C (under these

This study was performed in accordance with the Declaration of Helsinki, and with current European Community and U.S. Food and Drug Administration guidelines for good clinical practice. Prior to entry, all patients gave written informed

Course	No. of patients	Neutropenia (grade)					Thrombocytopenia (grade)					Anemia (grade)				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	33	17	0	3	5	8	18	1	6	3	5	22	4	5	1	1
2	27	15	1	1	3	7	17	1	3	1	5	17	2	3	3	2
3	13	5	1	0	5	2	6	2	1	2	2	6	3	0	3	1
4	10	5	0	1	3	1	6	1	1	1	1	6	2	1	0	1
5	7	3	0	2	1	1	3	1	2	1	0	3	2	1	1	0
6	6	5	0	1	0	0	5	0	0	0	1	5	0	1	0	0

^aToxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

conditions, melphalan was stable for 48 h) (14). The initial administered dose was 25 mg/m². Drug adjustment was then made using a population approach (16), with the aim of constraining the overall area under the plasma concentration-time curve (AUC) within 2.0-2.5 mg · h/l. This target AUC has been chosen according to the results first obtained during the phase I study (15). Thus, according to the hematological toxicity encountered during the previous cycle, the administered dose of the next course was: i) decreased to achieve an AUC of 1.5-2.0 mg · h/l for patients with intercurrent febrile neutropenia or grade 4 neutropenia lasting more than 7 days or grade 4 thrombocytopenia; ii) increased to achieve an AUC of 2.5-3.0 mg · h/l for patients with grade 0 or 1 neutropenia or thrombocytopenia; or iii) maintained in other cases. Courses were repeated every 28 days. All patients received prophylactic anti-emetic premedication with 5HT₃-receptor antagonists and corticoids before melphalan infusion.

Toxicity and response evaluation. Toxicity was assessed weekly according to the National Cancer Institute Common Toxicity Criteria scale (version 2). Tumor response was determined every 3 treatment cycles by clinical evaluation and an abdominopelvic computed tomography scan and/or any imaging technique used to measure the initial target(s), according to World Health Organization (WHO) criteria (17). Complete response (CR) was defined as the disappearance of all known target tumors, as confirmed by two consecutive examinations ≥4 weeks apart. Partial response (PR) was defined as a decrease of at least ≥50% in the sum of the total bidimensionally measurable surface areas of tumors, with no new lesions, confirmed by subsequent imaging examination ≥4 weeks later. A stable disease (SD) was characterized for patients as a <25% increase and <50% reduction in measurable disease with no new lesions, lasting at least 4 weeks. Patients with new lesions or a >25% increase of at least one measurable tumor, or clinical/radiological evidence of progression between scheduled evaluations had progressive disease (PD). Although serum CA125 level evolution was not used to evaluate response, it could be used to corroborate imaging assessments. Elevated serum CA125 levels had to return to normal for a CR. After the study treatment was discontinued, all patients were followed up at least every 3 months until death or last follow-up visit.

Results

Patient population. Patients (n=33) were enrolled and treated in this study from March 2001 to December 2004. The demographic, pretreatment and disease history characteristics of all 33 treated patients are detailed in Table I. The number of courses per patient ranged from 1 to 6. The median age was 58 years (range, 40-82), with 54.5% of patients having a performance status of 0-1. Most patients had advanced locoregional and/or metastatic disease at initial diagnosis (FIGO stage I to IV), with the majority of tumors (60.6%) being serous. The most common disease site was the peritoneum (24 patients), while 6 patients had liver metastases. All patients had received a prior cis/carboplatin-based regimen. In addition, 32 patients had been pretreated with taxane-containing chemotherapy regimens.

Treatment delivery and toxicity. A total of 96 courses of chemotherapy were administered (Table II). The mean dose of melphalan delivered was 25±5 mg/m², and the mean AUC value was 2.05 mg · h/l (range, 1.36-2.93 mg · h/l). The administered dose was increased by 20% after the first course for 9 patients (27%), maintained for 20 patients (61%) and decreased by 20% for 4 patients (12%). Hematological toxicity data are given in Table III. Grade 3-4 neutropenia was predominant, occurring in 37.5% of courses. Grade 3-4 thrombocytopenia occurred in 23.0% of courses, while grade 3-4 anemia occurred in 14.0% of courses. Overall, 3 patients required hospitalization for the management of treatment-related side effects because of febrile neutropenia, 6 patients required a platelet transfusion and 4 required a red blood cell transfusion during therapy.

The extramedullary toxicity included gastrointestinal complications (29 courses), asthenia (17 courses), alopecia (6 courses), and mucositis (4 courses). Nausea and vomiting were observed in 25% of courses. Diarrhea was observed in 5.2% of courses. Mild elevations of alkaline phosphatase and γ-glutamyl-aminotransferase (WHO grade I or II) were also observed. There were no treatment-associated deaths.

Response and survival. Of the patients, 4 received only one chemotherapy course, and 4 patients died. Thus, 25 patients were assessable for response and survival. Four (16%) PR

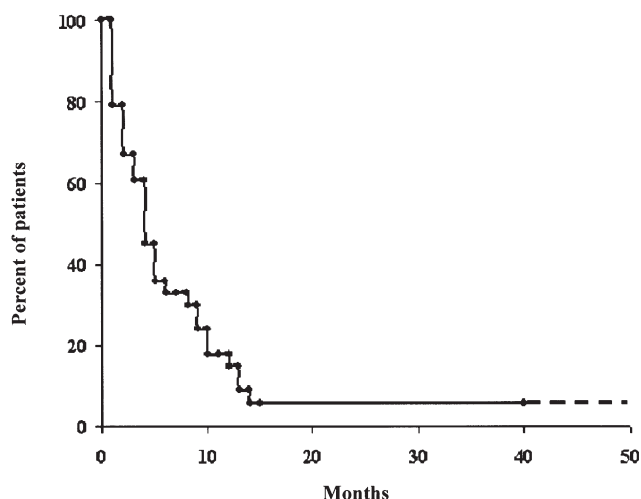


Figure 1. Actuarial survival time.

were observed and lasted 9, 10, 13 and 37 months, respectively. Three patients experienced SD for 8, 14 and 22 months, respectively. The actuarial survival time is presented in Fig. 1; the 1- and 2-year survival rates were 18% and 6%, respectively. At the time of the analysis, 2 patients were alive with progressive disease at 22 and 37 months, having received 6 and 4 courses of chemotherapy, respectively.

Discussion

Because only 10-15% of women who present with advanced ovarian cancer experience long-term remission, most patients are subject to repetitive treatment cycles, tumor responses and disease recurrences, or unchecked disease progression (18). Treatment of recurrent disease is palliative and carried out to: i) control disease-related symptoms; ii) limit treatment-related toxicity; iii) maintain or improve quality of life; iv) delay time to progression; and v) prolong survival. Over the past 30 years, there has been minimal improvement in the median survival of these patients. No standard chemotherapy regimen has been clearly established for the management of recurrent ovarian cancer. Thus, new chemotherapeutic treatments (19-24) or new modalities of administration of existing chemotherapy are required for patients who fail first-line treatment.

Data from early clinical studies using melphalan as second-line chemotherapy of stage III-IV ovarian carcinoma have been encouraging (25-32). In light of these results, a phase II study of melphalan as a single-agent infused over a 24-h period was initiated. The mechanism of action (phase specificity), pharmacokinetics (plasma half-life, volume of distribution and protein binding), stability in solution, and available preclinical data predict that many cytotoxic agents will have schedule-dependent antitumor activity and toxicity. Refinements in venous access options and ambulatory infusion pumps have stimulated increased interest in infusional delivery, owing to decreased logistic complexity with attendant increased patient convenience. Selected trials have suggested increased antitumor activity compared with conventional bolus infusion (33-37). In addition, infusional administration may improve the therapeutic index by decreasing toxicity (38-41). Thus,

the aim of this phase II study was to evaluate the safety and activity of melphalan administered over a 24-h period every 28 days in 33 pretreated advanced ovarian cancer patients. The toxicity profile did not differ greatly from that reported after a 1-h infusion (9) and was acceptable in such a heavily pretreated patient population. However, the thrombocytopenia reported in this study seemed not to be as significant as that reported by Davis-Perry *et al* after repeated oral administration of 7 mg/m² melphalan for 5 successive days (42). Indeed, these authors reported that grade I thrombocytopenia occurred in 19.7% of courses, grade II in 1.4% of courses and grade III in 5.6% of courses. However, comparable response rates were observed in the present study and a study published by Davis-Perry *et al* (42).

In conclusion, melphalan administered over a 24-h period in platinum- and taxane-resistant ovarian cancer patients appeared to provide some clinical benefits with manageable toxicity. Taking into account the small number of subjects included in that published trial, a randomized study is necessary to determine if melphalan administered over a 24-h period produces response rates superior to oral melphalan administrations.

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