DISCUSSION

The symptoms of intestinal obstruction in advanced malignancy are amongst the most distressing experienced by terminally ill patients, complicating 10% of hospice admissions [1]. In such patients, surgery offers the best chance for a sustained relief of symptoms, but is impractical where there is a limited outlook. In this situation, medical therapies are ineffective. Many of the conventional treatments for intestinal obstruction have side-effects. High dosage anti-emetics may have extrapyramidal toxicities, steroids have a plethora of side-effects and nasogastric tubes are uncomfortable. However, octreotide has no significant toxicity [2]. In this present study, 18/24 consecutive patients responded to octreotide given for intestinal obstruction due to a wide variety of different intra-abdominal malignancies. This high response rate is very encouraging, and almost certainly relates to the known effect of somatostatin and its analogues in reducing gastrointestinal secretion. It was apparent that if a response was not obtained with a dose of octreotide of up to 600 μg/day by subcutaneous infusion, further symptomatic improvement would not be obtained with a higher dosage, and should not be tried. Other authors have described transient discomfort at the site of injection of octreotide, but this was not reported by our patients. The efficacy and lack of toxicity of octreotide confirm our earlier findings [7], and suggest that it is a valuable addition to the palliative care armamentarium, and provides an impetus for a phase III investigation.

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Second-line Treatment with Ifosfamide and Carboplatin in Patients with Ovarian Carcinoma Relapsing After Treatment with Carboplatin

Stephen P. Dobbs, Claire Gribbin, Stephen Y. Chan and Eric M. Bessell

20 patients with ovarian carcinoma whose disease had relapsed (1–42 months, median 4 months) after showing either response or stable disease to carboplatin, were treated with ifosfamide (5 g/m² intravenously over 24 h, day 1) and carboplatin (200 mg/m² intravenously day 2) as second-line treatment. The mean number of treatment cycles was 3.5 (range 1–6). The major toxicities were thrombocytopenia (WHO grade 3/4, 25%), neutropenia (WHO grade 3/4, 40%) and encephalopathy (WHO grade 3/4, 15%). Overall response rate was 15% [complete response, 0; partial response, 3 (15%); no change, 5 (25%) and progressive disease, 12 (60%)]. The median survival from the date of second-line treatment was 7 months. This combination offers no advantage over either agent used alone.

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INTRODUCTION

IFOSFAMIDE [1, 2] AND carboplatin [3, 4] have both been shown to have activity in ovarian carcinoma relapsing after cisplatin therapy. Markman and Hoskins [5] have recently stressed the importance of analysing separately those patients with primary platinum-resistant ovarian carcinoma from those with potentially platinum-sensitive disease when investigating the activity of regimes in relapsed ovarian carcinoma. Primary platinum-resistant disease is defined as disease only showing less than partial response to first-line platinum therapy. Potentially, platinum-sensitive disease is disease showing at least a partial response and can be sub-divided into platinum-free intervals of less than 6 months, 6–12 months, and greater than 12 months

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between finishing first-line platinum therapy and starting second-line therapy. The median survival of patients treated with second-line therapy is usually 9–12 months from the date of starting therapy, but this depends on the degree of selection [1, 3, 5, 6].

The overall response rate for ifosfamide (1.2 g/m^2 per day for 5 days) and mesna in patients with either potentially platinum-sensitive or primary platinum-resistant ovarian carcinoma has been shown to be 20% [2], falling to 12% [1] in patients with primary platinum-resistant disease. In another study the overall response for carboplatin was 31% [3] in patients with potentially platinum-sensitive disease. A higher response rate of 48% was found by Kavanagh and Nicaise [4] in 25 patients treated in an M. D. Anderson trial.

Carboplatin (300 mg/m^2) and cyclophosphamide (100 mg/m^2 orally for 7 days) produced a response rate of 32% [6] in patients with potentially platinum-sensitive ovarian carcinoma with a platinum-free interval of greater than 3 months.

In this study , ifosfamide and carboplatin were combined in order to attempt to increase the response rate and survival of patients with ovarian carcinoma, relapsing after either showing stable disease or response to first-line carboplatin therapy.

PATIENTS AND METHODS

20 patients, whose disease had recurred after four to six cycles of carboplatin 400 mg/m^2 every 4 weeks (63 patients treated), were treated with ifosfamide [5 g/m^2, intravenously (i.v.) over 24 h with mesna 5 g/m^2, day 1] and carboplatin (200 mg/m^2, i.v. day 2). The cycles were given every 4 weeks. Mesna (1 g/m^2) was given as an i.v. bolus before the start of the ifosfamide infusion. Ifosfamide (1.67 g/m^2) and mesna (1 g/m^2) were administered every 8 h for 24 h, and then mesna (1 g/m^2) in dextrose saline (1 l) was given over 8 h, followed by carboplatin (200 mg/m^2) in normal saline (500 ml) over 30 min. Only patients with a normal full blood count and creatinine were eligible for second-line therapy. The median time between the completion of first-line carboplatin treatment and the commencement of ifosfamide/carboplatin treatment was 4 months (1–42 months).

The decision to use second-line chemotherapy was based on clinical evidence of recurrence rather than a rising CA125 level. The age range of the 20 patients was 34–71 years (median 54 years). 6 patients had stable disease (SD) after first-line carboplatin therapy (mean of 5.7 cycles), and 14 patients showed an objective response after first-line carboplatin therapy (six cycles) (Table 1). Of these 14 patients, the carboplatin-free interval was less than 6 months in 4 patients, 6–12 months in 6 patients, and greater than 12 months in 4 patients (Table 1). 5 of the 10 patients with a carboplatin-free interval of greater than 6 months received abdomino-pelvic radiotherapy following response to first-line carboplatin therapy.

Assessment of response

All 20 patients were evaluable for response, which was clinically assessed at the completion of treatment by WHO criteria [7]. A partial response (PR) was defined as a 50% or greater reduction in the size of all measurable lesions, including the complete disappearance of cytologically proven malignant effusions for at least 1 month without appearance of any new lesions. Measurements of CA125 were only used to support these data.

Table 1. Summary of results

Patient no.	Age (years)	No. of cycles of carboplatin	Abdomino-pelvic radiotherapy	No. of cycles of ifosfamide carboplatin	Carboplatin-free interval (months)	Response to second-line treatment	CA 125 with second-line treatment		Survival from date of second-line treatment (months)
							Before	After	
Primary platinum-resistant									
1	47	4	No	1	2	PD	135		1
2	71	6	No	3	2	SD			5
3	62	6	No	6	2	PR	8690	4290	7
4	56	6	No	5	2	SD	500	1290	15
5	42	6	No	6	2	PR	1155	693	28
6	34	6	No	4	3	SD	58	79	51
Primary platinum-sensitive									
7	54	6	No	6	3	SD	500	1290	8
8	48	6	No	3	4	PD	<10	69	4
9	54	6	No	1	4	PD	1790		1.5
10	65	6	No	3	3	PD	145	145	3
11	68	6	No	2	6	PD	860	1180	3
12	66	6	No	1	7	PD			0
13	48	6	Yes	1	8	PD	2398		3
14	54	6	Yes	3	8	PD	2680	15 850	6
15	56	6	No	6	9	PD	20	12	9
16	55	6	Yes	4	10	SD	483	374	7
17	47	6	Yes	6	15	PR	4500	177	12
18	57	6	No	2	20	PD	10 100	1280	1.5
19	50	6	No	1	29	PD	1700	1100	5
20	52	5	Yes	1	42	PD	206		6

Response was assessed clinically by WHO criteria. Measurements of CA125 were only used to support these data. PD, progressive disease; SD, stable disease, PR, partial response.

RESULTS

The mean number of cycles of ifosfamide/mesna and carboplatin given to the 20 patients with recurrent disease was 3.5 (range 1–6). Treatment was stopped either because of lack of response, or toxicity. No delays in treatment were necessary. In 2 patients, ifosfamide/mesna was stopped, and carboplatin (300 mg/m^2) was given alone for two and three cycles, respectively. There were no other reductions in dose. 3 patients had a PR with ifosfamide and carboplatin. A large, cytologically-proven, malignant pleural effusion resolved completely without recurrence, and the CA125 value fell from 4500 to 177 after six cycles. 2 patients had a partial response of a pelvic tumour (in one, the tumour was subsequently resected surgically, with a fall in CA125 from 1155 to 693, and in the other, CA125 fell from 8690 to 4290). 5 patients showed no change in their disease during chemotherapy (SD) and 12 patients had progressive disease (Table 1).

Toxicity

The major toxicity of ifosfamide/mesna and carboplatin was haematological. This was greater in those patients receiving abdomino-pelvic radiotherapy after first-line carboplatin treatment. WHO grade 3/4 neutropenia occurred in 4 (27%) of 15 patients not receiving radiotherapy, and 4 (80%) of 5 patients receiving radiotherapy. WHO grade 3/4 thrombocytopenia occurred in 2 (13%) of 15 patients not receiving radiotherapy, and 3 (60%) of 5 patients receiving radiotherapy. 3 patients experienced ifosfamide encephalopathy (1 grade 2; 1 grade 3; 1 grade 4). 3 patients had grade 1 renal toxicity. There were 2 probable treatment-related deaths in patients with progressive disease (1 from encephalopathy, grade 4, and 1 from thrombocytopenia, grade 4). 11 of the 20 patients had no significant toxicity in the categories mentioned above.

Survival

The median survival (Fig. 1) from the date of starting second-line therapy with ifosfamide/mesna and carboplatin was 7 months (range 0–51) The 1-year survival was 20%, with 2 patients (10%) surviving for more than 2 years (Table 1). There was no difference between the median survival of the 10 patients with primary platinum-resistant disease or a carboplatin-free interval (CFI) of less than 6 months, and the median survival of the 10 patients with potentially platinum-sensitive disease and a carboplatin-free interval of greater than 6 months (Fig. 1).

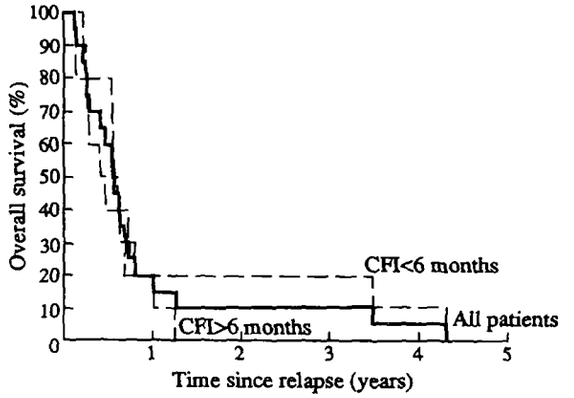

Fig. 1. Survival of 20 patients treated with ifosfamide/mesna (5 g/m^2) and carboplatin (200 mg/m^2) for relapse of ovarian carcinoma after first-line carboplatin therapy, and the survival according to the carboplatin-free interval (CFI). 10 patients CFI < 6 months; 10 patients CFI > 6 months.

DISCUSSION

Second-line chemotherapy for ovarian carcinoma is only palliative. Several studies have shown that the longer the period between completing the first-line treatment and starting the second-line treatment, the higher the response rate will be, and the more effective the palliation [3, 8, 9]. After first-line therapy with platinum regimes, the response rate for second-line treatment in primary platinum-resistant disease is only approximately 10% (ifosfamide/mesna 12% [1]; trimelamol 9.5% [10]; iproplatin 12% [11]), increasing to about 35% in those with potentially platinum-sensitive disease (carboplatin/cyclophosphamide, 32% [6]; iproplatin, 26% [11]; cisplatin, 43% [9]; carboplatin, 35–48% [3, 4]). The response rate with second-line platinum therapy increases with the platinum-free interval. Generally, in patients with a platinum-free interval of 5–12 months, the response rate was 27%, increasing to 33% for 13–24 months, and 59% for > 24 months. In patients not receiving any type of chemotherapy for 24 months after completing first-line treatment, the response rate increased further to approximately 77% [9].

The combination of ifosfamide (5 g/m^2) /mesna and carboplatin (200 mg/m^2) was chosen in an attempt to increase the response rate further. This combination has been studied in patients with relapsed and newly diagnosed ovarian carcinoma [12], where the recommended doses were carboplatin (400 mg/m^2) and ifosfamide (4 g/m^2).

In the present study the dose of carboplatin was lowered rather than the ifosfamide dose because the patients had all received carboplatin as first-line therapy.

In comparison with the studies quoted above, the response rate of 15% for ifosfamide/mesna and carboplatin in 20 patients relapsing after first-line carboplatin therapy (6 primary platinum-resistant, 14 potentially platinum-sensitive) is probably worse than the response rate which would be expected with either agent alone. The toxicity was acceptable in those patients not receiving abdomino-pelvic radiotherapy after first-line carboplatin therapy. The two possible treatment-related deaths occurred in patients with disease progressing on second-line therapy. Increasing the doses of both ifosfamide and carboplatin to produce a more effective regime would probably lead to unacceptable toxicity. Second-line therapy with carboplatin or cisplatin alone [3, 4], using $5HT_3$ antagonists, is acceptable as palliative treatment, particularly if the platinum-free interval is at least 3 months.

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Postoperative Chemotherapy Increases the Disease-free Survival Rate in Primary Gastric Lymphomas Stage IE and IIE

Felice Pasini, Achille Ambrosetti, Renata Sabbioni, Giuseppe Todeschini, Antonio Santo, Vittorio Meneghini, Giuseppe Perona and Gian Luigi Cetto

We describe 53 patients with primary gastric non-Hodgkin's lymphoma (38 stage IE,15 stage IIE) treated with surgery as a primary procedure. According to the Working Formulation, 13 cases had low, 21 had intermediate and 19 had high grade malignancy. 34 patients considered at high risk received postoperative polychemotherapy. The overall 10-year disease-related survival is 91%. Median follow-up is 52 months. 7 patients relapsed (13%). The 10-year disease-free survival rate of the 19 patients initially treated with surgery alone is 60%, as compared with 92% in the patients who also received chemotherapy ($P = 0.004$). However, overall survival did not differ between the two groups, since two-thirds of the patients who relapsed after surgery alone were rescued with chemotherapy. Stage, age, sex and histology did not correlate with survival. In our experience, surgery was an adequate first step procedure; the addition of chemotherapy significantly reduced relapses and increased the disease-free survival rate in patients with unfavourable prognostic factors.
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INTRODUCTION

PRIMARY EXTRANODAL non-Hodgkin's lymphomas (NHL) account for 10–30% of all NHL [1]. The most common site of extranodal lymphomas is the stomach where they represent approximately 5% of malignant tumours. Lacking randomised studies, the best treatment for primary gastric lymphomas (PGL) has not yet been defined. Some reports suggest that surgical resection may be sufficient treatment in stage IE and that surgical debulking significantly influences survival [2]. However, given that up to 60% of patients with stage IIE ultimately relapse when treated with surgery alone [3–6], there is general concern that surgery is not sufficient. The addition of radiotherapy can improve the local control [1], but recurrences were documented outside the irradiation field of up to 68% [3, 7].

In some studies postoperative chemotherapy alone or combined with radiotherapy enhanced the survival rate [4, 8–14]. Recent reports suggest that chemotherapy alone might be sufficient treatment, without major complications.

The aim of this study is to retrospectively evaluate the outcome of PGL, and the roles of surgery and postoperative chemotherapy.

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PATIENTS AND METHODS

Between 1975 and December 1990, 56 consecutive patients with PGL stages IE and IIE were referred to our department. Preoperative gastroscopy, with multiple biopsies, was performed in 52 patients. In 44 cases the procedure was diagnostic for