Principles and Management of Testicular Cancer. Baltimore, Williams & Wilkins, 1986, 387–396.
19. Connors JM, Klimo P, Voss N, Fairey RN, Jackson S. Testicular lymphoma: improved outcome with early brief chemotherapy. *J Clin Oncol* 1988, 6, 776–781.
20. Roche H, Suc E, Pons A, *et al*. Stage IE non-Hodgkin's lymphoma of the testis: a need for a brief aggressive chemotherapy. *J Urol* 1989, **141**, 554–556.
21. Reid G. Lymphoma of the testis—results of treatment 1960–77. *Clin Radiol* 1981, 32, 687–692.

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Response to Second-line Weekly Cisplatin Chemotherapy in Ovarian Cancer Previously Treated with a Cisplatin- or Carboplatin-based Regimen

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Response to a second-line weekly cisplatin chemotherapy in ovarian cancer previously treated with cisplatin- or carboplatin-based regimens was analysed in a clinical series observed between 1984 and 1991. Women who achieved pathological complete response or pathological optimal partial remission after first-line cisplatin- or carboplatin-based regimens were treated at recurrence or progression, occurring at least 4 months after first-line treatment, with second-line chemotherapy. A total of 72 women were included in the analysis. Second-line chemotherapy regimens were: cisplatin 1 mg/kg weekly for seven courses plus epirubicin 70 mg/m^2 intravenously (i.v.) every 3 weeks for three courses (28 subjects), cisplatin 1 mg/kg plus etoposide 90 mg/m^2 i.v. weekly for a total of seven courses (11 subjects) and cisplatin 1mg/kg weekly for nine courses plus carboplatin 250 mg/m^2 every 3 weeks for three courses (33 subjects). Of the 72 women, 22 (31%, 14 clinical, 8 pathological) had a complete response and 28 (39%), a partial response (24 clinical, 4 pathological). The 24-month cumulative survival probability was 63% in women with complete response, 32% in those who had partial response, but all the 22 non-responders died within 24 months from diagnosis of recurrence (log rank test $P < 0.05$). The frequency of complete response and partial response increased with the interval between first diagnosis and recurrence: among the 33 women who had recurrent disease to < 18 months from first diagnosis, complete response or partial response was obtained in 20 (61%) subjects, this figure was 67% (14 out of 21 women) among subjects who had recurrent disease between 18 and < 36 months from first diagnosis and 89% (16/18) among those who had recurrence ≥ 36 months. In comparison with women who had recurrence 4–< 18 months from first diagnosis, the OR of response was 1.3 (95% CI 0.4–4.1) for those who had recurrence between 18 and < 36 and 5.2 (95% CI 1.1–24.3) for those who had recurrence ≥ 36 months from surgery (χ^2_1 trend p < 0.05). Survival rate after the end of second line chemotherapy for women who relapsed 4–< 18 months, 18–< 36 or 36 months or more after surgery were, respectively, 24, 20 and 67% (log rank test, $P < 0.05$). Age at first diagnosis, histology, stage, and grading of the disease at first diagnosis and site of recurrence were not associated with response to second-line therapy.

Key words: ovarian cancer, second-line treatment, prognostic factors, chemotherapy
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INTRODUCTION

REPORTED PERCENTAGES of response to second-line chemotherapy in relapsing ovarian cancer range from about 25 to 70 per cent [1–7]. These differences may be attributable to differences in the characteristics of treated populations [6–8]. Definition of the determinants of responses to second-line chemotherapy may help in comparing results from different series and, from a clinical point of view, may be useful in establishing the prognosis of recurrent ovarian cancer and identifying women who may benefit from treatment.

We have analysed the response to second-line chemotherapy in ovarian cancer cases with recurrent disease, previously treated with platinum-based regimens.

Table 1. Distribution of 72 recurrent ovarian cancer cases according to response to second-line chemotherapy and selected characteristics, Milan, Italy 1984–1991

	Response			OR *(95% CI)
	Yes		No	
	Partial	Complete		
Progression-free interval after surgery (months)				
4–< 18	13	7	13	1†
18–< 36	8	6	7	1.3
≥ 36	7	9	2	5.2
χ^2_1 trend				$P < 0.05$
Site of relapse				
Abdominal	21	22	14	1†
Distant	7	—	8	0.4 (0.1–1.5)
Second-line chemotherapy regimen				
PEW	4	2	5	
EPW	10	8	10	
PCW	14	12	7	

*Partial or complete response versus no response. OR, odds ratio; CI, confidence interval. When CI includes unity the OR estimate is not statistically significant. †Reference category.

PATIENTS AND METHODS

Women observed between 1984 and 1991 at our centre who achieved pathological complete response or pathological optimal partial remission (≤ 5 mm) after first-line cisplatin- or carboplatin-based regimens were treated at recurrence or progression with second-line chemotherapy. Relapse or progression occurred at least 4 months after first-line treatment and was documented by imaging techniques or laparoscopy. Site of recurrence was abdominal in 57 cases (79%) and distant disease in 15 (21%). Patients were excluded if they had previous renal or neurological toxicity. A total of 72 women who met these criteria were included in the analysis.

Staging at first diagnosis was: stage I in 4 cases (6%), stage II in 6 cases (8%), stage III in 58 cases (81%) and stage IV in 4 cases (6%). All subjects underwent radical or debulky surgery at first diagnosis. Residual disease status after surgery was no disease in 9 cases (13%), < 2 cm in 17 cases (24%) and ≥ 2 cm in 46 cases (64%). After primary surgery, the women were treated with a chemotherapy regimen of platinum alone in 23 cases (32%), carboplatin alone in 4 cases (6%) and platin plus cyclophosphamide with or without doxorubicin in 45 cases (63%). Response to primary chemotherapy among the 62 women with residual disease after surgery was complete in 44 (71%) and partial in 18 (29%).

Second-line chemotherapy regimens were cisplatin 1 mg/kg weekly for seven courses plus epirubicin (EPW) 70 mg/m^2 intravenously (i.v.) every 3 weeks for three courses (28 subjects), cisplatin 1 mg/kg plus etoposide (PEW) 90 mg/m^2 i.v. weekly for a total of seven courses (11 subjects) and cisplatin 1 mg/kg weekly for nine courses plus carboplatin 250 mg/m^2 (PCW) every 3 weeks for three courses (33 subjects).

Response to treatment was assessed 2 months from the start of second-line treatment by standard imaging techniques (ultrasound or computer tomography) or minor surgery (laparoscopy), in case of no evidence of disease after second-line chemotherapy. Median of follow-up was 13 months (range 8–58).

This analysis includes 40 subjects already described elsewhere [8].

Data analysis

All analyses are based on data obtained before December 1992. Life-tables were calculated by the actuarial method and the curves were compared by the usual logrank test [9]. No deaths were observed before the end of second-line chemotherapy schedules. Odds ratios (OR) of response for various factors considered were computed with their 95% confidence interval (CI). When a factor could be classified in more than two levels, the significance of the linear trend was assessed by the Mantel test [8].

RESULTS

Of the 72 women, 22 (31%) had a complete response (14 clinical, 8 pathological) and 28 a partial response (39%, 24 clinical, 4 pathological). Median duration of response from the end of treatment was 15 months (range 2–57).

The 24-month cumulative survival probability was 63% in women with complete response, 32% with partial response, but all 22 non-responders died within 24 months of the diagnosis of recurrence (log rank test $P < 0.05$).

Frequencies of complete response and partial response according to progression-free interval after first-line chemotherapy, site of relapse and type of second-line regimen are presented in Table 1. The frequency of complete response and partial response increased with the interval between first diagnosis and recurrence: among the 33 women who had recurrent disease

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4–< 18 months from first diagnosis, 20 obtained complete response or partial response (61%). This figure was 67% (14/21) for women who had recurrent disease between 18 and < 36 months from first diagnosis, and 89% (16/18) among those who had recurrence ≥ 36 months. The corresponding OR of response was, in comparison with women who had recurrence 4–<18 months from first diagnosis, 1.3 (95% CI 0.4–4.1) for those who had recurrence between 18 and < 36 months and 5.2 (95% CI 1.1–24.3) for those who had recurrence ≥ 36 months from first diagnosis (χ^2_1 trend $P < 0.05$). We also computed the OR of response using the free interval classes proposed by Markman and colleagues [6] in comparison with subjects who had recurrence 4–12 months from first diagnosis, the OR of response to second-line chemotherapy was 0.6 (95% CI 0.1–2.6) and 2.6 (95% CI 0.4–16.7), respectively, in these who had recurrence > 12–24 and > 24 months from first diagnosis ($P = 0.07$).

Complete response or partial response was obtained in 43/57 women with abdominal recurrence (75%), and in 7 of the 15 (47%) with distant recurrence; the corresponding OR of complete response or partial response, in comparison with women with abdominal recurrence, was 0.4 (95% CI 0.1–1.5).

A total of 13 women did not complete second-line chemotherapy. Of those, 5 had progressive disease, 6 refused treatment and 2 reported toxicity.

Age at first diagnosis, histology, stage and grading of the disease at first diagnosis were not associated with response to second-line therapy (Table 2). In comparison with subjects with no residual disease after primary surgery, women with disease < 2 cm and ≥ 2 cm had, respectively, an OR of response of 3.3 (95% CI 0.3–20.1) and 2.5 (95% CI 0.3–9.9). The OR of response to second-line chemotherapy was 1.5 (95% CI 0.5–5.0) in women with complete response to first-line chemotherapy in comparison with those with partial (≤ 5 mm) response. These latter two findings were, however, not statistically significant, probably due to the small sample size.

We then analysed separately survival rates after the end of second-line chemotherapy for women who relapsed 4–< 18 months, 18–< 36 months or ≥ 36 months after first diagnosis:

Table 2. Distribution of 72 recurrent ovarian cancer cases according to response to second-line chemotherapy and selected characteristics at diagnosis. Milan, Italy 1984–1991

	Response			OR *(95% CI)
	Yes		No	
	Partial	Complete		
Age at first diagnosis (years)				
< 55	14	11	9	1†
≥ 55	14	11	13	0.7 (0.2–1.5)
Histology§				
Serous	17	15	10	χ^2_3* heterogeneity
Endometroid	7	3	8	Not significant
Other	4	4	3	
Stage at diagnosis				
I–II	2	3	5	1†
III–IV	26	19	17	2.6 (0.7–10.1)
Grading				
1	0	0	1	1†
2	7	9	3	
3	21	13	18	0.5 (0.1–1.6)
Residual neoplasm after primary surgery (cm)				
No	2	3	5	1†
< 2	8	5	4	3.3
≥ 2	18	14	13	2.5
χ^2_1 trend				P = non-significant
First-line chemotherapy regimens				
Monochemotherapy	8	8	11	1†
Polychemotherapy	20	14	11	2.1 (0.8–5.9)
Response to first-line chemotherapy‡				
Partial	7	5	6	1†
Complete	19	14	11	1.5 (0.5–5.0)

*Partial or complete response versus no response. OR, odds ratio; CI, confidence intervals. When CI includes the unity the OR estimate is not statistically significant. †Reference category. ‡Stage III and IV only. §Data for 1 patient missing.

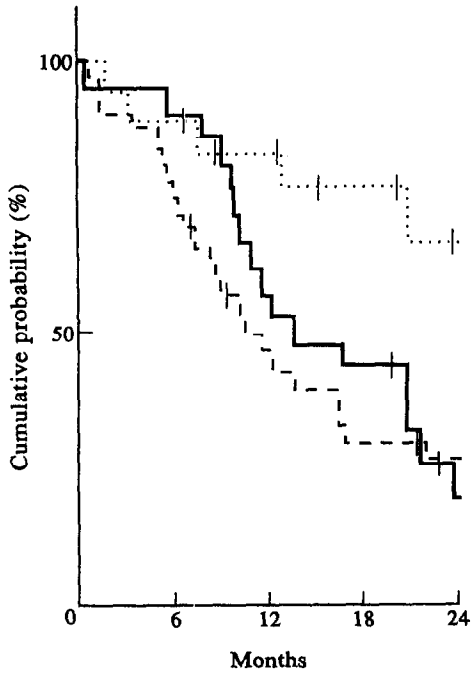

Figure 1. Cumulative overall survival according to progression-free interval after surgery. [--- 4– < 18 months (n = 33); —— 18– <36 months (n = 21); ··· ≥ 36 months (n = 18)].

survival was, respectively, 24, 20 and 67% (log rank test $P < 0.05$, Figure 1).

On the whole, the toxicity of those intensive treatments was acceptable: 59 patients finished the planned therapy with a median time of 53 days (range 43–86) in the seven courses treatments (PEW, EPW) and 67 days (range 63–96) in the nine courses treatment (PCW). An analysis of toxicity is showed in Table 3; no renal or ototoxicity was observed.

DISCUSSION

In this series, the determinant of response to second-line chemotherapy in ovarian cancer cases was the progression-free interval after primary surgery. Women who responded to retreatment had significantly longer median survival than non-responders. The latter finding is not necessarily attributable to a treatment effect, but may also be discussed in terms of selection. Women who did not respond to treatment may be subjects with worse general clinical conditions. However, all patients had a Karnowsky index ≥ 90 at the start of second-line chemotherapy. This analysis was designed to assess determinants of response. The three schedules used as second-line chemotherapy were not randomly assigned, so this study does not provide a basis for comparing the responses to different treatments.

Table 3. Toxicity of second-line treatments. Milan, Italy 1984–1991

	WHO grading		
	2 (%)	3 (%)	4 (%)
Haematological			
Leucopenia	15.2	29.1	2.7
Thrombocytopenia	19.4	22.2	8.3
Anaemia	26.3	16.6	4.1
Other			
Alopecia	11.1	33.3	—
Emesis	33.3	31.9	—
Stomatitis	13	2.7	—
Constipation	6.9	1.3	—
Paresthesias	6.9	4.1	—
Pulmonary	11.1	—	—

Our results are consistent with the scanty published data. An approximately 3-fold higher response rate to a second-line cisplatin-based regimen was reported in women with a disease-free interval longer than 24 months, in comparison with those with an interval of 12 months or less, in a series of 72 subjects at the Memorial Sloan-Kettering Cancer Center of New York [6]. Similar estimates were reported from the U.K. [7]. An overall response rate of 70% (31% complete and 39% partial responses) to a second-line cisplatin-based regimen, in women relapsed 6 months after primary surgery and first-line treatment with cisplatin- or platinum-based regimens, confirms the favourable rates of response to second-line chemotherapy reported in previous series [1]. However, this series includes cases who had already shown responsiveness to platin-based regimens. These findings confirm evidence from other cancer sites that some malignant cells remain sensitive despite the fact that they were not killed during first-line chemotherapy [6]. In addition, the lack of association between response and characteristics of ovarian cancer at first diagnosis is consistent with previous data [11].

All three regimens were well tolerated: less than 20% of women failed to complete the prescribed cycles, and no marked difficulties were observed in women who completed retreatment as regards dose delivery or compliance, and toxicity was largely similar to that reported for first-line chemotherapy with standard doses [12].

In conclusion, this analysis confirms that the progression-free interval from first-line chemotherapy is the major determinant of response to second-line chemotherapy in relapsing or progressing ovarian cancer. In clinical practice, time to progression or relapsing after primary surgery may be a useful indicator for deciding which chemotherapy to administer for relapsing ovarian cancer.

1. Thigpen JT, Vance RB, Khansur T. Second-line chemotherapy for recurrent carcinoma of the ovary. *Cancer* 1993, **71**, 1559–1564.
2. Seltzer V, Vogi S, Kaplan B. Recurrent ovarian carcinoma: retreatment utilizing combination chemotherapy including *cis*-diamminedichloroplatinum in patients previously responding to this agent. *Gynecol Oncol* 1985, **21**, 167–176.
3. Van der Burg MEL, Hoff AM, Van Lent M, Rodenberg CJ, Van Putten WLJ, Stoter G. Carboplatin and cyclophosphamide salvage therapy for ovarian cancer patients relapsing after cisplatin combination chemotherapy. *Eur J Cancer* 1991, **27**, 248–250.
4. Markman M, Rothman R, Hakes T, *et al.* Second-line cisplatin (C) treatment (RX) in patients with ovarian cancer (OC) previously treated with cisplatin. *Proc Am Soc Clin Oncol* 1990, **9**, 155 (abstract 599).
5. Williams LL, Fudge M, Burnett LA, Jones HW. Salvage carboplatin therapy for advanced ovarian cancer previously treated with cisplatin. *Am J Clin Oncol* 1992, **15**, 331–336.
6. Markman M, Rothman R, Hakes T, *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991, **9**, 389–393.
7. Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. *Gynecol Oncol* 1990, **36**, 207–211.
8. Zanaboni F, Scarfone G, Presti M, Maggi R, Borello C, Bolis

G. Salvage chemotherapy for ovarian cancer recurrence: weekly cisplatin in combination with epirubicin or etoposide. *Gynecol Oncol* 1991, 43, 24–28.
9. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, 35, 1–39.
10. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel–Haenszel procedure. *J Am Stat Assoc* 1963, 58, 690–700.
11. Belinson JL, Lee KR, Jarrell MA, McClure M. Management of epithelial ovarian neoplasms using a platinum-based regimen: a 10-year experience. *Gynecol Oncol* 1990, 37, 66–73.
12. Gruppo Interregionale Cooperativo Oncologico Ginecologico. Randomised comparison of cisplatin with cyclosphosphamide/cisplatin and cyclophosphamide/doxorubicin/cisplatin in advanced ovarian cancer. *Lancet* 1987, ii, 353–359.

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Clinical Evaluation of Serum Tissue Polypeptide-specific Antigen (TPS) in Non-small Cell Lung Cancer

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M3 is an epitope of the tissue polypeptide antigen detectable in the serum by immunoradiometric assay. This epitope is referred to as tissue polypeptide-specific antigen (TPS). We examined the pretreatment TPS level of 160 non-small cell lung cancer (NSCLC) patients and 71 patients who suffered from non-malignant pulmonary diseases. The upper limit of normal values was 140 U/l. Using this cutoff, the sensitivity and specificity were 36 and 90%, respectively. The TPS was significantly higher in NSCLC patients with an advanced stage, a mediastinal lymph node involvement or a poor performance status. This level was significantly higher in the group of patients for whom the disease proved to progress during chemotherapy. In univariate analysis, patients with a high TPS level proved to have a shorter survival than patients with a TPS ≤ 140 U/l. In Cox's model analysis, performance status, stage of the disease and serum TPS were the only significant prognostic variables. The low sensitivity of TPS precludes its use for diagnosis. However, the pretreatment TPS level adds information to the management of NSCLC inasmuch as it predicts a low sensitivity to chemotherapy and a poor prognosis.

Key words: non-small cell lung cancer, tissue polypeptide-specific antigen, chemotherapy, prognosis
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INTRODUCTION

THE TREATMENT of non-small cell lung cancer (NSCLC) is one of the most important challenges of medical oncology [1]. In patients with local disease, surgery can achieve a high rate of cure [2]. However, the majority of patients present with a more advanced disease for which combined modality treatments, such as radiotherapy and chemotherapy, are the subject of permanent reassessment [3].

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In inoperable NSCLC, seven trials have been conducted to compare the use of chemotherapy with the best supportive care available (for review see [4]). All these studies demonstrate a 10–20-week survival improvement in patients receiving chemotherapy. However, this survival advantage was significant only for trials which included a sufficient number of patients. Thus, the survival improvement induced by chemotherapy in NSCLC is hitherto probably modest. As chemotherapy might be responsible for an impairment of quality of life, particularly in non-responding patients, new markers able to predict prognosis and response to therapy might be useful.

Several serum tumour markers, such as tissue polypeptide antigen (TPA) [5], carcino-embryonic antigen (CEA) [6] or more recently CYFRA 21-1 [7], have been investigated in an attempt to determine their sensitivity, specificity and applicability in NSCLC. One of the most extensive experiences in this field is