Is pretreatment hemoglobin level a predictor of complete response to salvage chemotherapy for recurrent platinum-pretreated ovarian carcinoma?

A. Gadducci[1], S. Cosio[1], A. Fanucchi[1], L. Tanganelli[2], P. F. Conte[2], R. Cristofani[3], A. R. Genazzani[1]

[1]Department of Procreative Medicine, Division of Gynecology and Obstetrics;
[2]Department of Oncology, Division of Medical Oncology, S. Chiara Hospital;
[3]Department of Experimental Pathology, Medical Biotechnology and Epidemiology, University of Pisa, Pisa (Italy)

Summary

Purpose of investigation: The aim of this retrospective study was to correlate some patient characteristics at relapse, including also baseline hemoglobin levels, with complete response rate and survival following second-line chemotherapy for recurrent platinum-pretreated ovarian carcinoma.

Methods: The investigation was conducted on 63 patients who received salvage chemotherapy with different agents for clinically detectable recurrent ovarian carcinoma following initial surgery and first-line platinum-based chemotherapy. Some patient characteristics at relapse (patient age, serum CA 125 level, baseline hemoglobin level, number of recurrence sites, ascites, platinum-free interval, and treatment-free interval) were related to complete response rate to salvage chemotherapy and survival after recurrence. Median baseline hemoglobin level was 11.6 g/dl (range, 7.5-15.0 g/dl).

Results: Second-line chemotherapy obtained a complete response in 17 (27.0%) patients and a partial response in 11 (17.5%), whereas stable disease and progressive disease were detected in 19 (30.1%) and 16 (25.4%) patients, respectively. By univariate analysis, complete response rate was related to baseline hemoglobin level ($p = 0.0019$), platinum-free interval ($p = 0.0012$) and treatment-free interval ($p = 0.0048$). Multiple logistic regression showed that platinum-free interval ($p = 0.0107$) and baseline hemoglobin level (0.0312) were independent predictors of complete response. Patients with baseline hemoglobin levels >11.6 g/dl had a 5.338 higher chance of obtaining a complete response when compared to those with lower hemoglobin values. The platinum-free interval was the only independent prognostic variable for survival after recurrence ($p = 0.0141$), whereas baseline hemoglobin level was not related to survival at univariate nor at multivariate analysis.

Conclusions: Baseline hemoglobin level is an independent predictor of complete response to salvage chemotherapy in patients with recurrent platinum-pretreated ovarian carcinoma. Attention must be paid to anemia correction in these patients, with the aim of improving both the chance of response to salvage treatment and the quality of life.

Key words: Second-line chemotherapy; Recurrent ovarian carcinoma; Hemoglobin; Platinum.

Introduction

Ovarian carcinoma is the leading cause of death among gynecologic malignancies. Paclitaxel (TAX)/platinum-based regimens are able to achieve an objective response in 60-80% of patients with advanced disease, but the majority of them will relapse after initial chemotherapy and will be candidates for salvage treatment [1-9]. Several drugs are currently available for second-line chemotherapy [9-28], and platinum-free interval is generally considered as the best predictor of response to salvage treatment [9, 10, 29-31]. However, other variables have been correlated with response rate and survival of patients with recurrent ovarian carcinoma [9, 12, 31-33]. Some authors have recently suggested a predictive role for baseline hemoglobin levels in these patients [12, 32, 33]. Advanced solid malignancies are frequently hypoxic due to the structural and functional abnormalities of the tumor microvasculature, the increased diffusion distances and the tumor-associated anemia [34]. Hypoxia and anemia can make solid tumors resistant to irradiation and chemotherapy.

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The aim of this retrospective study was to correlate some patient characteristics at relapse, including also baseline hemoglobin level, with complete response rate and survival following second-line chemotherapy for recurrent platinum-pretreated ovarian carcinoma.

Materials and Methods

This study assessed 63 patients who received salvage chemotherapy for clinically detectable recurrent or progressive ovarian carcinoma following initial surgery and first-line platinum-based chemotherapy. The time frame during which the patients had their initial diagnosis of ovarian carcinoma ranged from March 1994 to March 2001.

Tumor stage and histological diagnosis of each case were determined according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) and the histological typing system of the World Health Organization (WHO), respectively. Tumors were graded as well (G1), moderately (G2), or poorly (G3) differentiated.

At the end of primary chemotherapy, second-look laparotomy was suggested to advanced ovarian carcinoma patients who were clinically free of disease or who had residual disease which seemed to be surgically resectable at clinical, ultrasonographic, and radiological evaluation. After clinical and/or surgi-

cal reassessment, the majority of advanced ovarian carcinoma patients received further chemotherapy.

All patients were periodically followed by physical examination, abdominal-pelvic ultrasound, chest X-ray, and serum CA 125 assay. Further examinations were performed when indicated. Asymptomatic patients with rising CA 125 levels were strictly investigated with clinical, ultrasonographic and radiological investigations.

Salvage chemotherapy at recurrence was given without well-defined protocols. Patients who first underwent macroscopically complete surgical cytoreduction at the time of recurrence were not included in this study, that conversely enrolled three patients who received salvage chemotherapy following suboptimal surgical cytoreduction which left clinically evident tumor residuum. All patients were followed until they died or until March 2002.

Median follow-up of survivors from the start of salvage chemotherapy was 13.5 months (range, 2-79 months).

Some patient characteristics at relapse (patient age, serum CA 125 level, baseline hemoglobin level, number of recurrence sites, ascites, platinum-free interval, and treatment-free interval) were related to complete response rate to salvage chemotherapy and survival after recurrence. Platinum-free interval was defined as the interval time between the last cycle of platinum-based chemotherapy and the clinical detection of recurrent disease. Treatment-free interval was defined as the interval time between the last cycle of any chemotherapy and the clinical detection of recurrent disease.

Statistical Methods

The statistical package SAS, release 6.7, was used for computations.

Rates of complete response to salvage chemotherapy were compared to explicative variables using Pearson's χ^2 test (or two-tailed Fisher's exact test when appropriate). Multiple logistic regression was carried out to investigate the relationship among the probability of achieving a complete response and the explanatory variables.

The cumulative probability of survival from the entry (defined as the start of salvage chemotherapy) was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables. A multiple regression analysis based on the Cox proportional hazard model was used to jointly test the relative importance of variables as predictors of survival times.

Results

At diagnosis FIGO Stage was I in two patients, II in three, III in 44, and IV in 14. Histologically, 45 carcinomas were serous, nine endometrioid, five undifferentiated, three mucinous, and one was a clear cell carcinoma. Tumor grade was G1-2 in 20 patients and G3 in 43.

First-line treatment consisted of six cycles of TAX (175 mg/m^2 3-hour infusion) + carboplatin (CBDCA) AUC 5-6 (every 3 weeks) in 20 patients, epirubicin (EPIDOX) 75 mg/m^2 + TAX (175 mg/m^2 3-hour infusion) + CBDCA AUC 6 (every 4 weeks) in 20, cyclophosphamide (CTX) (600 mg/m^2) + EPIDOX (60mg/m^2) + cisplatin (CDDP) (50 mg/m^2) (every 3 weeks) in 13 , CTX (600 mg/m^2) + CDDP (75 mg/m^2) (every 3 weeks) in two, and single-agent CBDCA AUC 6 (every 3 weeks) in eight.

The two patients with FIGO Stage I ovarian carcinoma were clinically free of disease after the sixth cycle of adjuvant platinum-based chemotherapy, did not undergo second-look surgery and did not receive any further treatment until clinical detection of recurrence.

One patient with FIGO Stage II and three patients with FIGO Stage III-IV disease developed tumor progression during first-line chemotherapy. Moreover one patient with FIGO Stage III-IV carcinoma had clinically detectable stable disease at the end of chemotherapy.

These five patients were considered to be platinum-refractory. Of the other 56 patients with FIGO II-IV tumor, 36 were clinically free of disease and 20 obtained a partial response after the sixth cycle of chemotherapy. A second-look laparotomy was performed in 29 patients: 12 were in pathological complete response, four had microscopic residual disease, four had macroscopic residual disease that was completely cytoreduced, eight had macroscopic residual disease that was not completely cytoreduced, and one patient was found to have progressive disease.

Further chemotherapy was given to 41 of the 56 patients with FIGO Stage II-IV ovarian carcinoma who had received six cycles of first-line regimen. It consisted of three-weekly TAX (175 mg/m^2 3-hour infusion) in 23 patients, weekly TAX (60 mg/m^2 1-hour infusion) in four, CBDCA AUC 6 (every 3 weeks) in 11, CDDP (75 mg/m^2) in two, and TAX (175 mg/m^2 3-hour infusion) + CBDCA AUC 6 (every 3 weeks) in one patient.

Table 1 shows patient characteristics at the time of clinical detection of relapse. The recurrence was considered to be single if it involved the pelvis or abdomen or retroperitoneal lymph nodes or one distant site, and multiple if it involved more than one of these sites.

Table 1. — *Patient characteristics at the time of clinical detection of recurrence.*

Age (median, range):	63 years (43- 82 years)
Serum CA125 level (median, range):	224 U/ml (9-3800 U/ml)
Baseline hemoglobin level (median, range):	11.6 g/dl (7.5-15.0 g/dl)
Number of recurrence sites	
single	31
multiple	32
Ascites	
yes	20
no	43
Platinum-free interval (months)	
0	5
1-6	15
7-12	19
>12	24
Treatment-free interval (months)	
0	7
1-6	24
7-12	15
>12	17

Recurrent disease involved the pelvis in 19 (30.1%) cases, the abdomen in 31 (49.2%), retroperitoneal lymph nodes in 21 (33.3%), and distant sites in 18 (28.6%). The sites of distant disease included lung (3 cases), pleura (5 cases), liver (8 cases), bone (1 case), groin lymph nodes (2 cases), brain (1 case), spleen (1 case), and skin (1 case).

Table 2 reports the second-line chemotherapy given to the 63 patients with recurrent ovarian carcinoma.

Overall, second-line chemotherapy obtained a complete response in 17 (27.0%) patients and a partial response in 11 (17.5%), whereas stable disease and progressive disease were observed in 19 (30.1%) and in 16 (25.4%) patients, respectively.

By univariate analysis, a complete response rate was related to baseline hemoglobin level (p = 0.0019), platinum-free interval (p = 0.0012), and treatment-free interval (p = 0.0048) (Table 3).

A very high correlation existed between the platinum-free interval and treatment-free interval (r = 0.97531, p < 0.0001). Therefore only the platinum-free interval, but not the treatment-free interval, was included in the multiple logistic regression.

The platinum-free interval (p = 0.0107) and baseline hemoglobin level (p = 0.0312) were found to be independent predictors of complete response to salvage chemotherapy (Table 4). It is worth noting that patients with baseline hemoglobin levels > 11.6 g/dl had a 5.338 higher chance of obtaining a complete response when compared to those with lower hemoglobin values.

With the log-rank test survival after recurrence was related to the platinum-free interval (p = 0.0014) (Figure 1), treatment-free interval (p = 0.0003) (Figure 2), and ascites (p = 0.0047) (Figure 3), but not baseline hemoglobin level (p = ns) (Figure 4), patient age, serum CA 125 level, and number of recurrence sites (data not shown).

Only the platinum-free interval, and not the treatment-free interval, was included in the Cox model.

Table 2. — *Second-line chemotherapy in recurrent ovarian carcinoma by platinum-free interval.*

	Platinum-free interval		
	0-6	7-12	> 12
3-weekly TAX (175 mg/m²)	4	1	–
T (1.5 mg/m² day 1-5)	3	2	–
D (40-50 mg/m²)	3	4	–
EPIDOX (90 mg/m²)	1	–	–
Weekly TAX (60 mg/m²)	4	2	–
IFO (1 g/m²/day 14-day infusion)	2	2	–
GEM (1 g/m²/day 1,8,15)	1	1	–
Oral VP-16 (50 mg/day)	1	–	–
EPIDOX (90 mg/m²)+ TAX (175 mg/m²)	1	–	–
CBDCA (AUC 5-6) or CDDP (75 mg/m²)	–	5	16
CDDP (75 mg/m²) + CTX (600 mg/m²)	–	1	1
TAX (175 mg/m²) + CBDCA AUC 5	–	1	7

TAX, paclitaxel; T, topotecan; D, doxil; EPIDOX, epirubicin; IFO, ifosfamide; GEM, gemcitabine; VP-16, etoposide; CBDCA, carboplatin; CDDP, cisplatin; CTX, cyclophosphamide.

Table 3. — *Variables predictive of complete response to second-line chemotherapy (univariate analysis).*

Variables	Patients n.	Response to second-line chemotherapy CR n.	PR n.	SD n.	PD n.
Patient age (years)					
> 63	30	11	4	8	7
≤ 63	33	6	7	11	9
		(p = ns)			
Serum CA125 (U/ml)					
> 224	31	9	2	12	8
< 224	32	8	9	7	8
		(p = ns)			
Hemoglobin (g/dl)					
≤ 11.6	35	4	8	11	12
> 11.6	28	13	3	8	4
		(p = 0.0019)			
Ascites					
yes	20	3	4	9	4
no	43	14	7	10	12
		(p = ns)			
Recurrent sites					
multiple	32	5	7	10	10
single	31	12	4	9	6
		(p = ns)			
PFI (months)					
≤ 12	39	5	4	15	15
> 12	24	12	7	4	1
		(p = 0.0012)			
TFI (months)					
≤ 12	46	8	4	17	16
> 12	17	9	6	2	0
		(p = 0.0048)			

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFI, platinum-free interval; TFI, treatment-free interval.

Table 4. — *Variables predictive of complete response to second-line chemotherapy (multiple logistic regression).*

Variable	Parameter estimate	Standard error	Wald χ^2	p value	OR	95% CI
Intercept	-1.3189	0.9306	2.0085	0.1564		
PFI	1.8752	0.7350	6.5099	0.0107	6.522	1.545-27.541
Hbg	1.6748	0.7774	4.6420	0.0312	5.338	1.163-24.494

OR, Odds ratio; 95% CI, 95% Confidence Interval; PFI, platinum-free interval; Hbg, hemoglobin.

The platinum-free interval was found to be the only independent prognostic variable for survival after recurrence (χ^2, 6.0299; p = 0.0141; hazard ratio, 0.404; 95% confidence interval, 0.196-0.833).

Discussion

The platinum-free interval is a major determinant of response to second-line chemotherapy in platinum-pretreated ovarian carcinoma patients [9, 10, 29-31]. Patients are usually distinguished as platinum-refractory (progression under platinum-based therapy), platinum-resistant (relapse within 6 months), and platinum-sensitive (relapse after 6 months) [9, 29]. The longer the platinum-free interval, the higher response rate to platinum-retreatment. Markman *et al.* [10] reported that response rate to

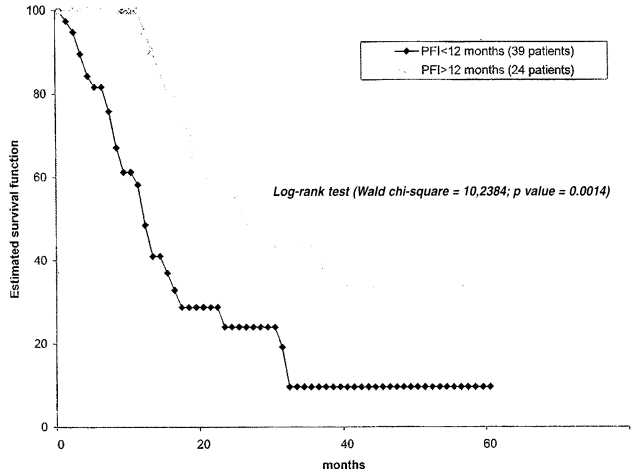

Figure 1. — Overall survival after second-line chemotherapy in patients with recurrent ovarian carcinoma by platinum-free interval (PFI).

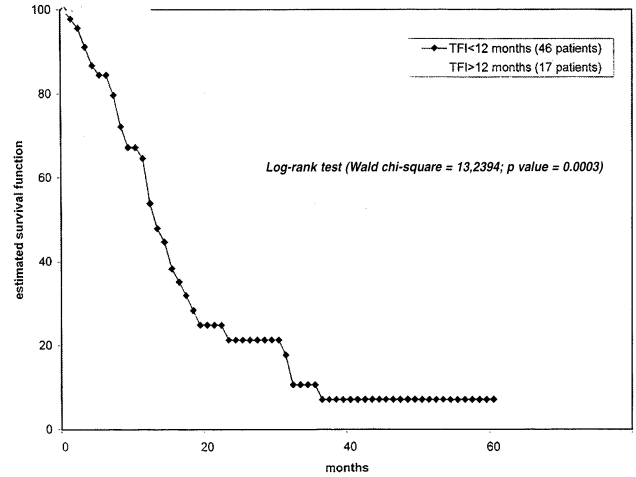

Figure 2. — Overall survival after second-line chemotherapy in patients with recurrent ovarian carcinoma by treatment-free interval (TFI).

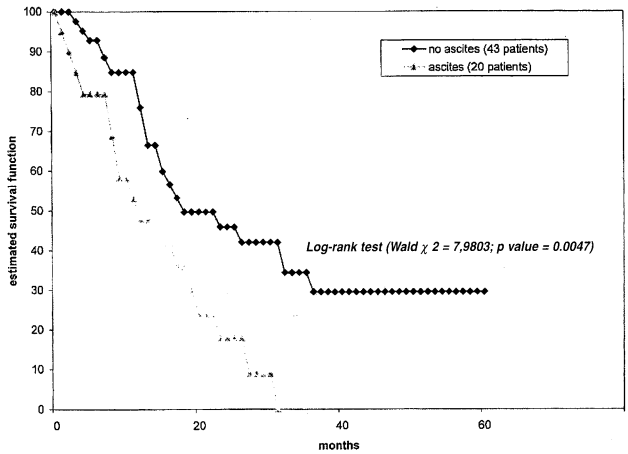

Figure 3. — Overall survival after second-line chemotherapy in patients with recurrent ovarian carcinoma by ascites.

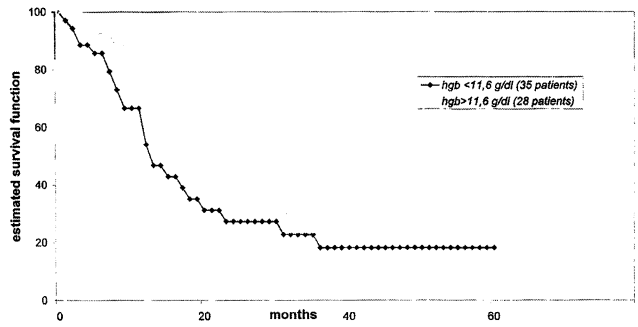

Figure 4. — Overall survival after second-line chemotherapy in patients with recurrent ovarian carcinoma by hemoglobin levels (Hgb).

second-line CDDP/CBDCA ranged from 27% for patients with a cisplatin-free interval of 5-12 months to 59% for those with an interval longer than 24 months. Moreover these authors found that response rate was 77% in patients without any treatment for more than 24 months from the completion of their initial therapy.

Several drugs, other than CDDP and CBDCA, are available for second-line therapy. For instance, collected data from the literature reported objective response rates of 13-28% for TAX [11, 12, 17, 19, 20, 25], 17-33% for topotecan [17, 23, 24], 20-33% for EPIDOX [13, 14], 17-26% for doxil [18, 23, 28], 11-19% for gemcitabine [16, 21], 16-29% for oxaliplatin [15, 25], and 23-28% for docetaxel [26, 27]. The activity of most agents is higher in patients with platinum-sensitive disease. Since the response rate and duration to different single-agents are similar, patient convenience, toxicities from prior treatment, and side-effects play a major role in drug selection for patients with recurrent ovarian carcinoma [9].

Besides the platinum-free interval, other variables have been assessed as predictors of response to second-line chemotherapy, such as tumor histology [12, 32] tumor burden [12, 32, 33], and hemoglobin level [12, 32, 33]. For instance the re-analysis of a large series of platinum-pretreated ovarian carcinoma patients included in four studies showed that serous histology ($p = 0.009$), fewer sites of disease ($p = 0.003$), and smaller tumor size ($p = 0.001$) were independent predictors of response to second-line treatment using different drugs, whereas normal baseline hemoglobin level was a predictor of response at univariate but not at multivariate analysis [32]. In a series of 52 ovarian carcinoma patients who were given doxil after failing initial platinum-based chemotherapy, tumor size and baseline hemoglobin level were the main predictive factors for time to failure, and these variables plus performance status were the main predictive variables for survival [33].

In cancer patients anemia is due to both tumor itself and myelosuppressive treatments [34, 35]. Besides decreasing the functional capacity and quality of life of these patients, anemia can impair the response to irradiation and chemotherapy. Severe anemia is common in ovarian carcinoma patients receiving postoperative-TAX/platinum-based chemotherapy [36], and moreover recent data seem to show that pretreatment serum hemoglobin level is an independent prognostic variable for patients with this malignancy [37]. In fact in a multivariate analysis on 206 ovarian carcinoma patients the relative risk of death was significantly associated with decreasing pretreatment serum hemoglobin levels, which seemed to suggest that marked tumor anemia is an indicator of the presence of biologically aggressive tumor cell clones [37]. In anemic cancer patients treatment resistance could be, at least partially, prevented or overcome by anemia correction, thus resulting in better tumor control and in better overall survival [34]. In the present investigation, the platinum-free interval ($p = 0.0107$) and baseline hemoglobin level ($p = 0.0312$) were independent predictors of complete response to salvage chemotherapy for recurrent platinum-pretreated ovarian carcinoma.

It is worth noting that patients with baseline hemoglobin levels > 11.6 g/dl had a 5.338 higher chance of obtaining a complete response when compared to those with lower hemoglobin values. The platinum-free interval was the only independent prognostic variable for survival after recurrence ($p = 0.0141$), whereas baseline hemoglobin level was not related to survival at univariate nor at multivariate analysis. In our study complete response rate and survival were not assessed by type of salvage chemotherapy, but, in any case, the literature data showed that response rate and duration to different single-agents are similar [9]. Patients with platinum-sensitive disease have a good chance of response to platinum retreatment, whereas in platinum-resistant patients different agents produce short-lived response rates ranging from 5 to 30% approximately. Therefore these latter patients should be encouraged to enter well-designed clinical trials [38].

In conclusion, baseline hemoglobin level is an independent predictor of complete response to salvage chemotherapy in patients with recurrent platinum-pretreated ovarian carcinoma. Attention must be paid to anemia correction in these patients, with the aim of improving both the chance of response to salvage treatment and the quality of life.

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Address reprint requests to:
A. GADDUCCI, M.D.
Department of Procreative Medicine
Division of Gynecology and Obstetrics
University of Pisa
Via Roma, 67
56127 Pisa (Italy)