Cancer Chemother Pharmacol (1990) 25: 355–360

Cancer Chemotherapy and Pharmacology

Efficacy and safety of high-dose cisplatin and cyclophosphamide with glutathione protection in the treatment of bulky advanced epithelial ovarian cancer

Francesco Di Re, Silvia Bohm, Saro Oriana, Gian Battista Spatti, and Franco Zunino

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

Summary. Recent efforts to improve the response rates in advanced ovarian cancer with the use of high-dose cisplatin have been limited by unacceptable toxicity. Based on experimental and clinical studies indicating that reduced glutathione (GSH) is a protective agent against cisplatin-induced toxicity, a new high-dose regimen including GSH as a chemoprotector was designed in an attempt to improve the efficacy and therapeutic index of cisplatin. A total of 40 consecutive patients with stage III (bulky) and IV ovarian carcinoma were treated with cisplatin (40 mg/m^2 daily for 4 consecutive days) and cyclophosphamide (600 mg/m^2 i.v. on day 4). The treatment was repeated every 3–4 weeks for five courses unless progression or severe toxicity occurred. Before each cisplatin administration, patients received GSH (1,500 mg/m^2) i.v. over 15 min, with a standard i.v. hydration (2,000 ml fluid) without diuretics. Debulking surgery was initially attempted in 18 patients and, after 2–3 courses, in 16 patients; it could not be carried out in 6 patients. Three patients were not evaluable for response because they prematurely discontinued their treatment. In all, 23 patients (62%) achieved complete clinical remission (negative second-look laparotomy in 16), with an overall (complete + partial) response rate of 86%; 2 patients achieved disease-free status following second surgery. Nausea/vomiting was the most severe acute toxic effect; myelosuppression was acceptable. Renal impairment was effectively prevented by GSH. Neurotoxicity that was not associated with motor dysfunction was the most significant cumulative toxicity in patients (24/32) receiving 4–5 courses. The results of this study indicate that the use of GSH is a safe new method for high-dose cisplatin administration. This regimen is well-tolerated and very effective in ovarian cancer patients with bulky disease and warrants further evaluation.

Introduction

In epithelial ovarian cancer, a multidisciplinary approach has improved treatment results [1]. Although cytoreductive surgery plays a critical role in the response to subsequent therapy [7], systemic therapy has a central part in the management of the advanced disease [19]. Moreover, application of "optimal" surgery, which is critically dependent on the stage and extent of disease, is not possible at presentation in >50% of cases [14, 22].

Since the introduction of cisplatin in the treatment of advanced disease, response rates have improved [6, 14], but in patients with bulky stage III and stage IV disease, they remain disappointingly low and long-term survivors comprise a minority of patients [1, 14]. This observation has stimulated further attempts to improve first-line therapy. Evidence of a dose-response effect for cisplatin [15] has suggested the use of high doses of this drug. Aggressive initial approaches appear to be justified, in view of evidence that only patients obtaining a pathologically complete response have some expectancy of long-term survival and considering the low efficacy of second-line regimens.

However, high-dose cisplatin is a controversial approach since it is one of the most toxic regimens ever tested [15]. The toxicity of high-dose regimens remains a major obstacle to progress in the treatment of advanced ovarian cancer. The use of intensive hydration protocols (6 l/day) and hypertonic saline has enabled the escalation of the cisplatin dose beyond 120 mg/m^2 with acceptable nephrotoxicity [16]. These administration procedures have obvious risks and disadvantages and remain problematic in clinical practice. In addition, high-dose cisplatin therapy is associated with varying degrees of peripheral neuropathy, which becomes a limiting factor in most patients [2, 9, 16].

Since cisplatin is such a useful drug in the treatment of ovarian cancer, efforts to explore other methods of reduction of nephrotoxicity and overall toxicity have continued. There is currently great interest in the possibility of using thiols to reduce the serious side effects of cisplatin and improve its therapeutic index [5]. Although some sulfur-containing compounds have proven to be effective in reducing cisplatin toxicity [18], the major problem in their clinical use remains the lack of selective protection of normal tissues, since they can also reduce the antitumor effects of cisplatin [11]. On the basis of their affinity to heavy metals, these nucleophilic compounds are expected to inactivate the toxic species of cisplatin. Among sulfur-containing compounds, reduced glutathione (GSH) fulfills some fundamental requirements for an antidotal agent since, in ex-

Offprint requests to: Franco Zunino, Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milan, Italy

perimental models using well-tolerated dose levels, it effectively prevents the nephrotoxic effects of cisplatin without interfering with its cytotoxic and antitumor activity [23, 24].

Based on these experimental data and on preliminary clinical observations indicating that GSH is well tolerated and does not interfere with antitumor activity [13], a pilot study was carried out to test the safety and efficacy of high-dose cisplatin and GSH in patients with bulky ovarian cancer.

Patients and methods

From November 1986 to May 1988, 40 consecutive patients with ovarian cancer entered into a pilot study with high-dose cisplatin (160 mg/m^2) plus cyclophosphamide. To be eligible, patients had to have epithelial carcinoma of the ovary as histologically confirmed by the Department of Pathology of our institute. They all had International Federation of Gynecology and Obstetrics (FIGO) stage III (bulky) or IV disease and none had previously been treated. Stage III patients with minimal residual disease (<2 cm in diameter) following "optimal" debulking surgery were not eligible for the protocol. Only two patients with borderline-size tumors were included, since they had multiple infiltrating lesions. In these patients, the disease was not easily measurable by clinical or radiological examinations. With the exception of these two cases, all patients had clinically and radiologically measurable bulk disease. All of the patients had satisfactory bone marrow, liver and kidney function as indicated by leukocyte and platelet counts of at least 4,000 and 150,000/mm^3, respectively, normal serum bilirubin, SGOT, SGPT and creatinine levels. They were required to have a Karnofsky performance status of >70. The main characteristics of the patients are shown in Table 1. Informed consent was obtained from each patient.

Table 1. Patient characteristics

	Patients (*n*)
Total	40
Median age in years (range): 50 (28–68)	
Stage:	
III	26
IV	14
Histology:	
Serous	28
Endometrioid	3
Undifferentiated	2
Mixed	3
Unclassified adenocarcinoma	3
Clear cell	1
Grade:	
1	1
2	20
3	14
Ungraded	5
Disease before chemotherapy:	
≤2 cm	2
2–5 cm	10
5–10 cm	4
>10 cm	24
Measurable disease	38

Aggressive cytoreductive surgery was included in the treatment protocol. Chemotherapy was begun as soon as patients had recovered from primary abdominal exploration (i.e., laparoscopy or laparotomy for biopsies in 15 and 7 patients, respectively) or after initial surgery (debulking), when possible (18 patients). In 15 patients with massive disease (in general, stage IV), cytoreductive surgery was not judged to be feasible on the basis of the clinical and radiological examinations; thus, laparoscopy instead of laparotomy was carried out to avoid delay of the chemotherapy. When initial debulking was attempted, residual extensive disease was still present postoperatively, despite maximal surgical efforts. When surgery was not initially feasible, debulking was attempted after 2–3 courses of chemotherapy in responsive patients; in six patients, debulking surgery was never possible. All surgical procedures were carried out by the same group of surgeons.

The regimen consisted of cisplatin (40 mg/m^2 given daily for 4 consecutive days as a 30-min infusion in 250 ml normal saline) and cyclophosphamide (600 mg/m^2 given as an i.v. bolus on day 4 only). GSH (1,500 mg/m^2) was given in 100 ml normal saline over 15 min before each cisplatin administration; it was provided by Boehringer Mannheim Italia (Milan, Italy) as a sterile, freeze-dried powder in 20 ml-vials containing 2,500 mg drug.

Standard i.v. hydration (2,000 ml fluid) without diuretics was used: 2 h prior to initiation of the cisplatin infusion, patients were hydrated with 1,000 ml normal saline to which 20 mEq KCl and 15 mEq $MgSO_4$ were added. Post-hydration was continued for 2 h with 1,000 ml normal saline containing 20 mEq KCl. Cycles were repeated every 3–4 weeks for a total of five courses or until disease progression or severe toxicity occurred.

In the absence of tumor progression, all patients underwent second-look laparotomy or surgery when required. Objective tumor responses to treatment were defined clinically in patients with clinical progression and by surgery in those who underwent secondary exploration. To assess surgical histological response, second-look laparotomy included multiple biopsies from areas of macroscopic disease, from sites of previous disease, and from any suspicious or high-risk areas (diaphragm, paracolic gutters and pelvic peritoneum). A complete response was considered to be pathologically documented if all the biopsies and washings were negative. A clinically complete response was defined as the complete disappearance of disease detectable by physical and/or radiological examination. A partial response was defined as a reduction of >50% in all measurable lesions at second surgery.

Toxicity was assessed on the basis of routine hematological and biochemical parameters. A complete blood count and platelet count as well as values for serum blood urea nitrogen (BUN), creatinine and electrolytes were obtained before and after treatment, daily during treatment and weekly between courses. Liver function tests were done every 3 weeks. Audiograms were obtained before treatment when possible or shortly after the first course and at treatment completion.

Table 2. Clinical response

	Number of patients with tumors (size in cm) before chemotherapy				Total[a]
	≤2	2–5	5–10	>10	
Complete response	2	9	4	8	23 (62)
Partial response	0	0	0	9	9 (24)
No response[b]	0	1	0	4	5 (14)

[a] In parentheses, percentage of evaluable patients (n = 37)
[b] Two patients had stable disease after three courses

Results

Response

Of the 40 patients treated with high-dose cisplatin plus cyclophosphamide, 37 were evaluable for response and toxicity. These patients were considered to be evaluable since they received a minimum of 3 courses for a total of 167. The three non-evaluable patients discontinued their treatment: one withdrew from this study to seek alternative therapy, another refused further treatment and was lost to follow-up after three courses and yet another was withdrawn from the study for myocardial ischemic disorders (unrelated to treatment).

Although the planned five courses could safely be given to most patients (25/37), 7 (all responders) received only four courses. In two of these patients, the cisplatin dose in the fifth course was decreased to 90 mg/m^2 because of a delayed recovery from myelotoxicity. In three patients, the second-look laparotomy was carried out after only four courses because of early neurotoxic manifesta-

Table 3. Pathological evaluation and follow-up of clinically disease-free patients at treatment completion[a]

	Patients (n)	% of evaluable patients (n = 37)
Clinical complete response	23	62
Underwent second-look laparotomy	20	
Second-look laparotomy negative	16	43
NED following surgery	2	
Microscopic residual disease	2	
Total NED at treatment completion	21	57
Clinical complete response without second-look laparotomy	3	
Pathologically complete response	16	
NED following second surgery	2	
Current status:		
Alive	23/23 (survival: from 10+ to 27+ months)[b]	
Still NED	19/21 (disease-free interval: from 10+ to 27+ months)	
Relapse	2/21 (disease-free interval: 12 and 17 months)	

[a] In all, 17 patients received 5 courses, 5 patients received 4 courses, 1 patient received 2 courses
[b] Survival was calculated from the date of the completion of chemotherapy
NED, no evidence of disease

Table 4. Follow-up of patients with persistence of disease after high-dose cisplatin

	Patients (n)	Second surgery[a]	Current status:	
			Alive	Dead
Partial response	9[b]	3	5	4
Stable disease	2[c]	0	2	0
Disease progression	3[d]	0	0	3
Total	14		7	7
Survival range (months)[e]			10+ – 18+	4–12

[a] Patients (n) with minimal residual disease following second surgery at the completion of chemotherapy
[b] Seven patients received five courses; two patients received four courses
[c] One patient received three courses and the other, five courses
[d] These patients received three courses
[e] Survival was calculated from the date of the completion of chemotherapy

Table 5. Toxicity

Toxic effect	Patients (n)
Gastrointestinal:	
Nausea only	0
Nausea and vomiting, controllable	0
Intractable vomiting	40[a]
Life-threatening	0
Leukopenia (cells/mm^3):	
3,000–4,000	4
2,000–3,000	14
1,000–2,000	13
<1,000	2
Thrombocytopenia (cells/mm^3):	
100,000–150,000	14
50,000–100,000	12
20,000– 50,000	0
<20,000	2
Anemia (hemoglobin, g/100 ml):	
9.5–10.9	17
8.0– 9.4	14
<7.9	7
Nephrotoxicity:	
Creatinine 1.5–2.0 mg/dl	3
Peripheral neuropathy[b]:	
Grade 1	17
Grade 2	7
Grades 3 or 4	0
Ototoxicity (audiogram abnormalities)	11
Visual disturbances	0
Liver enzyme elevations	8

[a] Generally occurred on day 4
[b] According to ECOG toxicity criteria.

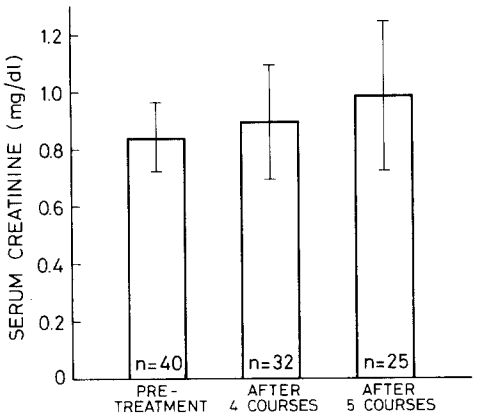

Fig. 1. Serum creatinine concentrations in patients with ovarian cancer receiving high-dose cisplatin therapy. Bars = SD

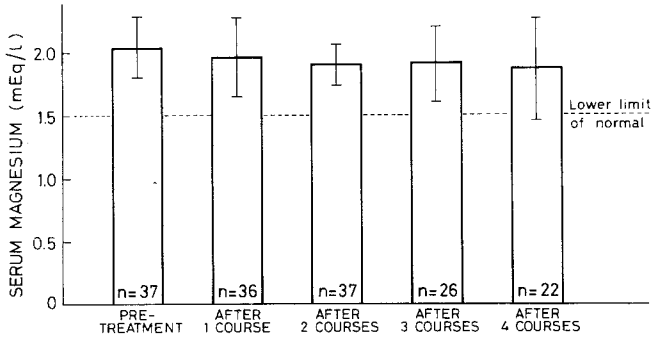

Fig. 2. Mean serum magnesium concentrations in patients with ovarian cancer receiving high-dose cisplatin therapy. The magnesium concentration was determined immediately before each subsequent course (*pre-treatment* values referred to determinations before the first course). Bars = SD

tions (two cases), and hepatotoxicity (one case). Two patients requested cessation of the treatment before the last course. Four patients discontinued therapy because of progressive disease or lack of response after three courses. One patient who discontinued treatment after two courses was evaluable for response, since she achieved complete clinical remission and was still progression-free after 19 months.

The results of therapy are summarized in Table 2. Of the 37 evaluable patients, 23 (62%) achieved a complete clinical response. In 16 patients, including 2 with unmeasurable disease, a complete response was documented pathologically. Three patients refused second-look laparotomy and four had persistence of microscopic disease (Table 3); two of the latter were rendered disease-free following second surgery. All clinically disease-free patients were alive from 10+ to 27+ months after the completion of treatment, and 19 of these remained free of disease. Details concerning the treatment and survival of patients with persistent disease are presented in Table 4. Most of these patients had massive disease (>10 cm in diameter) before chemotherapy. This observation is consistent with the prognostic importance of the volume of pretreatment disease and, therefore, the primary debulking.

Table 6. Cumulative toxicity

Toxic effect[a]		Number of patients given a cumulative dose of (mg/cm^2):		
		480	640	800
Peripheral neuropathy:	grade 1	3		14
	grade 2		3	4
Ototoxicity		1	4	6
Nephrotoxicity:	grade 1		1	2

[a] Graded according to ECOG toxicity criteria

Toxicity

Treatment with high-dose cisplatin plus cyclophosphamide in combination with GSH was well tolerated. The main side effects are listed in Table 5. As expected, a mild to moderately severe degree of nausea and vomiting (generally confined to days of treatment) was uniformly observed in all cases but was partially controlled with the use of antiemetics except on day 4 of treatment. This side effect appeared to be somewhat more severe than that observed with standard doses of cisplatin. Several patients had protracted nausea or vomiting on the day after chemotherapy. In general, the patients were hospitalised for 2 days after each course.

In spite of the moderate amount of fluids used in the i.v. hydration protocol (2 l/day), only three patients developed a mild, transient elevation of serum creatinine (up to 1.6–1.8 mg/dl). The mean serum creatinine value at the start of therapy was 0.83 mg/dl; after five courses of therapy, this value was 0.98 mg/dl (Fig. 1). Since tubular injury produced by cisplatin may cause hypomagnesemia as a consequence of renal magnesium wasting, even when the serum creatinine level remains normal, serum magnesium levels were determined during therapy (Fig. 2). The mean serum magnesium concentration was not significantly reduced (from 2.04 mEq/l before therapy to 1.87 mEq/l after four courses). In general, electrolyte imbalance was not observed; only one patient developed transient hypocalcemia (associated with an increase in serum creatinine of up to 1.8 mg/dl).

Hematologic toxicity was acceptable. The median nadir WBC count was 2300/mm^3 and the median nadir platelet count was 121,000/mm^3. Two patients had absolute leukocyte counts of <1,000/mm^3, which were not complicated by fever or infections. Only two patients had a platelet count of <20,000/mm^3 without clinical evidence of bleeding. Anemia (with a decrease of >3.0 g/dl hemoglobin in seven patients) required transfusion in about 20% of our patients. Mild, reversible neuropathy was a frequent (24/32 patients), cumulative side effect after 4–5 courses of high-dose cisplatin (Table 6). Even when neurotoxicity was manifested by severe paresthesias (seven patients), it was not associated with motor dysfunction, and no patient required assistance in walking. Since a delayed onset of severe and disabling neurotoxicity is associated with high-dose cisplatin therapy [2], no patient received more than five courses.

Hepatic enzyme alterations were also observed in eight patients; they had showed moderate elevations of serum

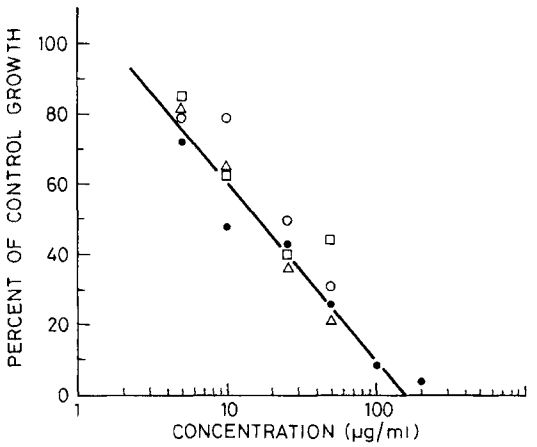

Fig. 3. Dose-response curve for cytotoxic activity of cisplatin given alone (●) or in combination with GSH at different concentrations – (○), 25 μg/ml; (△), 50 μg/ml; (□), 100 μg/ml) – on a human ovarian cancer cell line. This permanent cell line was established from a mixed histological epithelial ovarian cancer. Cells were exposed to cisplatin for 1 h. When cells were treated in combination with GSH, the thiol compound was added to medium 30 min before cisplatin. After treatment, cells were cultured in drug-free medium for 72 h and then counted in a Coulter counter

transaminases that were generally associated with milder elevations of γ-glutamyl-transpeptidase and, in three cases, with elevations of alkaline phosphatase. These changes were generally observed after 3–4 courses and returned to normal levels by around 30 days post-treatment, except in two patients who presumably had anicteric viral hepatitis. The etiology of these hepatic dysfunctions remains unclear.

Discussion

The rational bases for the use of GSH as a protector against cisplatin-induced nephrotoxicity are: (1) the preferential concentration of GSH in the kidney following i.v. administration (the kidney is recognized as being the main organ of GSH metabolism) [24]; (2) extracellular GSH does not cross the cell membrane and is not taken up by the majority of cells (except in tissues with expression of γ-glutamyl-transpeptidase on the cell surface) [12]; (3) since GSH is rapidly removed from the blood [21], direct interaction between GSH and cisplatin is unlikely in plasma.

The results presented in this study indicate that the use of GSH is a safe new method for delivering high doses of cisplatin. This method has obvious advantages in clinical practice: forced diuresis, intensive i.v. hydration and hypertonic saline may be avoided. Data are not available on the incidence and severity of nephrotoxicity following the administration of cisplatin without GSH on this schedule and with a hydration protocol comparable with that used in our study.

However, since it is well known that dose escalation above 120 mg/m^2 with standard hydration is precluded by an unacceptable incidence of nephrotoxicity [3], the absence of appreciable alterations of kidney function with this high-dose regimen using pre-treatment with GSH is excellent indirect evidence that GSH is an effective protector against cisplatin-induced toxicity. The efficacy of GSH in preventing renal damage is also emphasized by the lack of an appreciable loss of magnesium. Cisplatin-induced hypomagnesemia has been reported to be a frequent side-effect even at lower doses [20]. The observation that GSH enables the administration of 90 mg/m^2 cisplatin and a small volume of fluids (1,000 ml) without diuretics provides further indirect evidence that GSH has a protective action against renal damage [4]. Obviously, the degree of clinical benefit of GSH at standard cisplatin doses remains to be established.

An unexpected finding of this study was that the overall toxicity of this high-dose regimen was moderate. In particular, myelotoxicity was lower than that expected with high-dose cisplatin [15]. Even with the use of continuous 5-day infusion (i.e., the best-tolerated schedule for delivery of cisplatin [17], myelosuppression limited the cumulative dose/course to 150 mg/m^2 [10]. Similarly, although neurotoxicity was a frequent side effect, its incidence and severity was lower than that reported with the use of cisplatin doses in the range of 120–200 mg/m^2 [2, 9, 15]. The tolerability of our protocol enabled us to give most of our patients five courses. At very high doses of cisplatin (> 150 mg/m^2 per course), no more than three courses are recommended to avoid severe neuropathy [9]. Since the delayed development of severe neuropathy could be a major problem even with the use of GSH, the number of courses was limited to no more than five.

The efficacy and high degree of activity of this regimen supports the experimental observation that GSH is a selective protector [23, 24], since it does not interfere with the antitumor activity of cisplatin. Indeed, GSH did not interfere with the cytotoxic activity of cisplatin against ovarian tumor cells growing in vitro (Fig. 3). However, the high response rate for high-dose cisplatin with GSH pre-treatment was an unexpected finding in this traditionally poor-prognosis group of patients. In patients with bulky disease, conventional treatments have not produced a frequency of pathologically complete responses exceeding 20% [1, 19]. This study also supports the therapeutic value of chemotherapy regimens containing high-dose cisplatin in ovarian cancer [8, 15]. The lack of GSH interference with the antitumor effectiveness of cisplatin may be rationalised in terms of very limited GSH uptake by the tumor.

The therapeutic interest in this new approach is also suggested by the following observations. First, seven patients achieved clinically complete responses after only 2–3 courses. This finding was particularly intriguing in three patients with massive disease who did not receive initial debulking surgery. One patient was negative at laparotomy, and two patients with residual malignancy were rendered disease-free by surgery. Second, most of the patients achieving a partial response generally showed a marked reduction in tumor burden at the completion of chemotherapy.

Since the results of chemotherapy regimens in the treatment of advanced ovarian carcinoma are influenced by several factors, a comparison with more conventional protocols is difficult. However, since patients were selected for major, unfavourable prognostic factors (i.e., the volume of pre-treatment disease) [14], we believe that high-dose cisplatin plus cyclophosphamide, given with

GSH, is one of the most active protocols for advanced ovarian cancer.

At present, the short follow-up does not enable conclusions to be drawn on the survival of this poor-prognosis group. Preliminary observations from our initial series of 20 patients indicated a disease-free interval of >18 months in 8/10 patients in complete remission and survival of 75% at this time of follow-up. Thus, if this trend is confirmed, the high response rate is expected to be associated with improved results in terms of survival. In the treatment of advanced ovarian cancer with conventional drug combinations containing standard doses of cisplatin (50 mg/m^2), survival of around 65% was observed at 18 months [22]. Similar results have been reported in other clinical experiences [14]. However, it should be noted that these studies generally included patients with minimal residual disease (i.e., with a better prognosis) and survival was measured from the start of chemotherapy [22].

The precise role of this new approach in improving the therapy of advanced disease and the relative contribution of aggressive surgery have yet to be better established by detailed comparisons with the most effective conventional regimens in multicenter trials.

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Received 31 March 1989/Accepted 14 September 1989