Response to neo-adjuvant intraperitoneal and intravenous immunochemotherapy followed by interval secondary cytoreduction in stage IIIc ovarian cancer

B. Zylberberg[1], D. Dormont[2], S. Janklewicz[3], E. Darai[1], J. J. Bretel[1], C. Poncelet[1], J. L. Guillet[1], P. Madelenat[1]

[1]Bichat Hospital, 46 rue, H-Huchard, 75018 Paris; [2]CEA, Neurovirology Service, CRSSA, EPHE, BP. 6, 92265 Fontenay aux Roses cedex; [3]CHI Robert Ballanger, 93402 Aulnay sous Bois (France)

Summary

Design: The aim of this study was to determine the effect of intraperitoneal (ip) neo-adjuvant immunochemotherapy, followed by secondary interval cytoreduction in bulky ovarian carcinoma, considered inoperable at first exploratory laparotomy.

Patients and Methods: From 1980 to 1996, 13 naive patients with stage IIIc ovarian cancer underwent an initial laparotomy. Cytoreduction was judged too dangerous in these patients due to the large bulk of the tumor and the extent of peritoneal carcinomatosis. Simple biopsies were performed. The patients received an intraperitoneal cisplatin-based protocol monthly plus immunotherapy (DGZ).

The interval secondary cytoreduction was started either when the patients seemed to be in complete remission or after a minimum of 4 courses of chemotherapy if the patients' results were stagnant or deteriorated. Immunochemotherapy was then resumed for a total of up to 10 courses.

Results: At secondary cytoreduction, six patients were in complete remission as demonstrated histologically and cytologically. Seven patients were in incomplete remission. In six, debulking was completed without visceral resection. The seventh patient still had nodules more than 2 cm in diameter. Median overall survival was 57 months (range: 6-165).

Conclusion: Intraperitoneal immunochemotherapy was effective in bulky tumors, making optimal secondary cytoreduction possible in almost all cases.

Key words: Ovarian cancer; Stage IIIc; Intraperitoneal neoadjuvant chemotherapy; Immunotherapy.

Introduction

The most efficient therapeutic approach currently available for advanced ovarian carcinoma is based on optimal initial cytoreductive surgery followed by systemic platinum-based chemotherapy [1-4]. The aims of surgery are to provide a pathological diagnosis, to determine the FIGO (Fédération Internationale de Gynécologie Obstétrique) stage of the tumor as a prognostic factor and debulking (the most conservative possible of visceral resections), to increase the efficacy of chemotherapy [1, 2-5]. Adjuvant intravenous (iv) cisplatin-based protocols yield a 60 to 80% response in ovarian cancer [6-8]. However, in advanced forms more than 50% of patients relapse, and at five years, the survival rate rarely exceeds 25% [9-12]. Few data have been reported concerning first-line intraperitoneal (ip) chemotherapy in ovarian cancer [11-16]. Despite the pharmacological advantage of the ip administration, resulting in higher local drug concentrations for the same dose [13-16], ip therapy is mostly used after first-line iv treatment, as a second-line treatment, on small residual tumors, with the attendant risk of having to deal with cell lines resistant to the initial iv treatment [1-3, 13-16].

The main objection raised against ip chemotherapy is its inability to produce plasma drug concentrations similar to those obtained with intravenous administration of the same drug. It has also been criticised for the pooor penetration in the tumor by direct contact. Howell [17] demonstrated that by increasing the ip dose of cisplatin for example, using sodium thiosulfate to counteract nephrotoxicity, it is possible to achieve plasma concentrations higher than those achieved with the usual doses given intravenously. Although ip treatment destroys only a few millimeters of tumour, this destruction is repeated at each cycle of chemotherapy. In addition, after absorption into the capillaries of the peritoneum, the drugs are directly released into the systemic venous circulation. This double attack by external (contact) and internal (capillaries) routes appears to be more effective than attack by either one of these routes alone.

Recently, a randomized study has shown the benefits of first-line cisplatin-based chemotherapy by ip route [18]. Clear benefits from ip administration were observed in patients with microscopic and macroscopic disease.

Three studies have shown that iv neo-adjuvant chemotherapy increases survival [18, 20-21]. However, the value of ip neo-adjuvant treatment in advanced ovarian cancer has never been evaluated. Since 1980, after initial surgery, our patients with ovarian cancer have been treated by first-line combined ip and iv adjuvant immunochemotherapy [22-25]. Thirteen of the 68 stage IIIc patients, treated from 1980 to 1996, only underwent biopsies at initial laparotomy, because it was not possible to

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perform cytoreduction without risking severe damage. These patients were then treated by neo-adjuvant immunochemotherapy by combined ip and iv routes.

The aim of this study was to evaluate the value of this therapeutic strategy.

Patients and Methods

1) Patients

From 1980 to June 1996, 68 naive patients with common FIGO stage IIIc ovarian cancer underwent an initial exploratory laparotomy. Cytoreduction was optimal, without visceral resection, with a complete pathological response in 13 patients (19%) and was sub-optimal in 42 (62%).

For the remaining 13 patients (19%), only multiple biopsies were performed for histological diagnosis because it was not possible to carry out debulking without serious risk of visceral resection. This study concerns only the 13 patients with simple initial biopsies. The characteristics of these patients are summarized in Table 1. They had a WHO (World Health Organization) performance status of 0 to 2 and adequate cardiac, bone marrow and renal functions. All 13 patients had extensive diffuse carcinomatosis. Histologically, 11 of the 13 cystadenocarcinomas were serous papillary, one was endometrioid (patient no. 2) and one undifferentiated (patient no. 6).

For each patient the surgeon evaluated the largest tumoral mass (Table 1).

Chemotherapy protocols

Three successive protocols have been used since 1980 (Table 2).

In the second and third protocols, sodium thiosulfate, which counteracts the nephrotoxicity of cisplatin, has been used to enable us to increase the total dose of cisplatin from 90 to 200 mg/m^2 at each cycle.

DGZ is an extract from *vibro cholerae*, which we administered ip, as a form of immunotherapy, at a dose of 120 mg. The aim of this biological response modifier (BRM) therapy is to enhance the natural defenses of the organism thereby acting as an adjuvant of chemotherapy. Delivery into the peritoneum may be more efficient in eliciting a local immune response at the site of tumour development.

Protocol 1 was administered over three days, and protocols 2 and 3 over two days. Paclitaxel (3rd protocol) was administered intraperitoneally on the first day of treatment with 10 ml of 2% lidocaîne, in an infusion of 150 ml of normal saline, at the end to the creation of the artificial ascites.

For all 3 protocols, ip chemotherapy was administered in 2 liters of liquid (1 liter of normal saline and 1 liter of 5% glucose).

The technique used for ip infusion involved either a lumbar puncture needle or a needle with a spring-loaded blunt stylet for creating pneumoperitoneum at laparoscopy. During ip infusion (less than one hour) the patient was given iv 2 liters of 5% glucose for 24h with antiemetics, ifosfamid and sodium thiosulfate.

Interval secondary cytoreductive surgery

All 13 patients consented to interval secondary cytoreduction (ISCR). The date of the intervention was determined according to tumoral reduction as assessed by physical examinations, imaging (mainly ultrasound, CT scan and MRI) and monthly Ca 125.

Following this reintervention, initial chemotherapy was resumed for a total of up to 10 courses. If all 10 cycles had been administered before secondary cytoreduction, and if residual lesions would have been left by the intervention, a rescue protocol was planned but was not necessary in any case.

Table 1. — *Characteristics of the 13 stage IIIc patients.*

Age	
Median	54.9
Range	31-67
Histology	
Serous	11
Endometrioid	1
Undifferentiated	1
Size of the largest tumor	
5 to < 10 cm	7
≥ 10 cm	6
Peritoneal carcinomatosis	13

Table 2. — *Intraperitoneal neoadjuvant immunochemotherapy: protocols delivered in 13 patients with stage IIIc ovarian cancer.*

	ip route		iv route	
1st protocol	Doxorubicin:	40 mg/m^2		
(1980-1985)	Fluorouracil:	1000 mg/m^2		
n = 3 patients	Cisplatin:	90 mg/m^2		
	Bleomycin:	30 mg	Ifosfamid:	1300 mg/m^2
	DGZ:	120 mg		
2nd protocol	Cytarabin:	500 mg/m^2		
(1985-1994)	Fluorouracil:	1000 mg/m^2		
n = 7 patients	Cisplatin:	200 mg/m^2	Ifosfamid:	1300 mg/m^2
	Bleomycin:	30 mg	Sodium Thiosulfate:	26 g/m^2
	DGZ:	120 mg		
3rd protocol	Paclitaxel:	120 mg/m^2	Ifosfamide:	1300 mg/m^2
(> 1994)	Cisplatin:	200 mg/m^2	Sodium Thiosulfate:	26 g/m^2
n = 3 patients	DGZ:	120 mg		

Statistics

Overall survival and disease-free survival (DFS) were calculated according to the Kaplan-Meier method, and comparisons were made with the log rank test. Overall survival was calculated from the date of diagnosis of ovarian cancer, established at first laparotomy until death. DFS was calculated from the same initial date of diagnosis until relapse. The end point of the study was June 1999.

Results

The results are summarized in Table 3. At the end point, the median follow-up was 56 months (range: 6-165).

The 13 patients had received 4 to 10 courses of chemotherapy before ISCR (10 cycles n = 3 patients; 7 cycles n = 2; 6 cycles n = 5; 5 cycles n = 2; 4 cycles n = 1).

At the time of ISCR, six patients (nos. 2, 4, 5, 6, 11 and 13) were in complete remission as determined histologically and cytologically.

These six patients had undergone total hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy and multiple biopsies, especially in the areas described as involved at primary laparotomy.

Seven patients had residual lesions (incomplete remission), less than 0.5 cm in diameter in two patients (nos. 3 and 7), between 0.5 and 2 cm in three patients (nos. 1, 9 and 12), and more than 2 cm in diameter in two patients (nos. 8 and 10). In six of the seven patients, ISCR was

Table 3. — *Results of ip immunochemotherapy in 13 patients with stage IIIc ovarian cancer.*

Patients	Initial tumor size	Chemotherapy	Secondary cytoreduction		Chemotherapy	Relapses (months)	Alive (months)	Deceased (months)	CA 125	
	(cm)	Number of preoperative cycles	Complete remission	Incomplete remission	Number of postoperative cycles				Initial	Before SCR****
1	13x10	7		+ (1 cm)	3	56		85	ND	ND
2	> 10	7	+		3	153	165		ND	ND
3	> 10	6		+ (< 0.5)	4	10		17	ND	ND
4	> 7	6	+		3	54		59	ND	ND
5	> 10	6	+		4	30		55	1280	10
6	< 5	10	+		0		135		3045	5
7	> 5	6		+ (< 0.5)	4	17		33	3600	17
8	> 10	6		+* (> 2)	4	6	68**		270	162
9	> 10	4		+ (< 2)	6	No	36		215	4
10	> 8	5		+ (> 2)	5	13		17	788	42
11	6	10	+		0	47	57**		1370	10
12	> 7	5		+ (< 2)	0			6***	74	43
13	> 7	10	+		0	38		71	1684	35

*: Residual tumor of SCR; **: Alive with progressive disease; ***: Deceased post surgery; ****: Secondary cytoreduction; ND: Not determined

complete. For the seventh (patient no. 8), there were residual lesions more than 2 cm in diameter at the end of ISCR. After 4 courses of chemotherapy, this patient underwent a third surgical look which showed the persistence of four nodules of less than 1 cm in diameter on the liver surface. The patient has refused any further treatment. She is still alive 68 months after diagnosis, with rising CA 125 levels since the 59th month of follow-up.

Surgical morbidity

One patient died postoperatively from a mesenteric thrombosis. For the other 12 patients, no particular morbidity was observed.

Chemotherapy delivery

The patient who died of surgical complication had received 5 cycles of chemotherapy before surgery. Eleven patients were given the entire planned courses, and the remaining one (patient no. 4) refused the 10th cycle. Overall, 124 courses (95.4%) of the 130 initially planned were administered.

Toxicity

The systemic and local toxic effects are summarized in Tables 4 and 5, respectively.

Systemic toxicity:

There were no treatment-related deaths. Since the patients were given ondansetron, vomiting was no longer a problem. Two patients (15.3%) suffered two and three episodes of grade 3 vomiting [5 of 124 cycles (4%)]. No severe nephrotoxicity or peripheral neuropathy was observed except for grade 1 paresthesia of the limbs in seven patients, linked to the combination of paclitaxel and cisplatin, which lasted less than six months. We observed neither cardiac failure, nor cisplatin-related tinnitus or hearing loss. There were 17 episodes of grade 3 and 4 granulocytopenia of 124 cycles (13.7%) affecting five patients (38.4%). Infectious episodes with fever requiring antibiotics were observed 11 times (13.7%) in four patients (30.7%). These febrile episodes delayed the subsequent courses from 3 to 6 days, and 16 days in one case. It was never necessary to reduce the planned dose of chemotherapy.

Table 4. — *Frequency of systemic toxic effects during any course of treatment in 13 patients with stage IIIc ovarian cancer*

	Number of patients	Grade 2	Grade 3	Grade 4
Nausea vomiting				
Before ondansetron	6/6		5 (83.3%)	1 (16.7%)
Since ondansetron	4/7	2 (28.5%)	2 (28.5%)	
Nephrotoxicity	2/13	2 (15.3%)		
Granulocytopenia	8/13	3 (23%)	3 (23%)	2 (15.4%)
Thrombocytopenia	5/13	3 (23%)	2 (15.3%)	

Table 5. — *Frequency of local toxic effects during any course of treatment in 13 patients with stage IIIc ovarian cancer*

	Number of patients	Grade 2	Grade 3	Grade 4
Abdominal pain				
1st protocol	3/3	1	2	
2nd protocol	0/7			
3rd protocol	1/3	1		
Peritoneal adhesions	4 (30.7%)			

Local toxicity

Grade 2 and 3 abdominal pain occurred in three patients treated with the first protocol and this led us to abandon doxorubicin. With the second and third protocol, pain was rarely observed, and at a maximum of grade 1. One patient (7.6%) of the three treated with paclitaxel in the third protocol had abdominal pain. Minor adhesions were observed in four patients (30.7%) at ISCR.

Survival

Median overall survival from initial surgery was 57 months (range: 6-165) (Figure 1).

Five patients are alive, of whom three are disease-free. Median disease-free survival was 34 months (range: 6-165).

Of the six patients in complete pathological remission after neo-adjuvant chemotherapy at ISCR, two were alive and disease-free, with follow-up periods exceeding ten years (patients nos. 2 and 6). A third patient was alive, but had progressive disease (no. 11). The other three patients died respectively after 30, 38 and 54 months of follow-up (nos. 4, 9, 13).

Of the seven patients in incomplete remission at ISCR, two were alive (patient no. 9 clinically disease-free and patient no. 8 in relapse with follow-up periods of 36 and 68 months, respectively).

The six patients whose lesions disappeared before cytoreduction survived significantly longer than the seven patients with persistent lesions at ISCR (median 32 months vs median over 60 months, respectively) ($p<0.05$) (Figure 1).

The median survival time for the other 55 patients treated classically by adjuvant chemotherapy after initial surgery was more than 72 months for those who had optimal surgery (complete in 13 cases and with residual tumors of less than 0.5 cm in 10 cases) and 59 months for the 29 patients with residual tumors of more than 0.5 cm in diameter.

Statistically, there was no difference in survival between the 13 patients who had interval secondary surgery and the 29 patients with residual tumors of more than 0.5 cm in diameter after initial surgery. However, the surgical morbidity rate was much higher for the 29 patients who underwent surgery at first intention due to visceral resections with, in particular, 2 definitive colostomies.

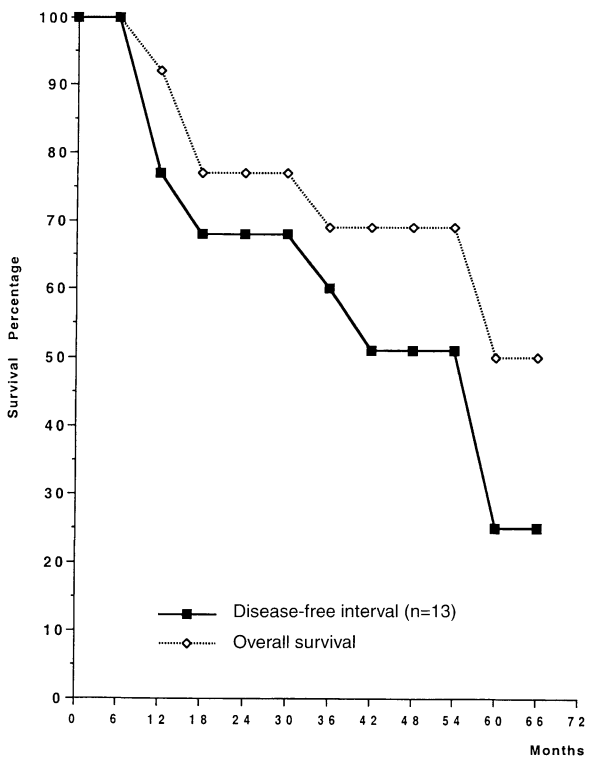

Figure 1. — Overall and disease-free survival in 13 patients with stage IIIc ovarian cancer treated with ip neoadjuvant immunochemotherapy.

Discussion

This study shows that in patients for whom optimal or suboptimal resection is not possible at initial surgery, without risk of major visceral damage, neo-adjuvant chemotherapy is feasible, with acceptable levels of morbidity and mortality.

The frequency of complications observed was low: 13.7% of grade 3 and 4 granulocytopenia and 8.8% febrile episodes in 124 courses of chemotherapy (30.7 and 38.4%, respectively of the 13 patients).

Despite use of a dose twice that usually utilized (200 mg/m^2 every 28 days) and a total dose more than tripled (2000 mg/m^2 instead of 600 mg/m^2), no severe nephrotoxicity or hearing problems were observed.

This study demonstrates a lower morbidity of chemotherapy drugs administered by the ip route, especially for platin [18], the nephrotoxicity of which is counteracted by sodium thiosulfate given intravenously [18].

In the study by Alberts *et al.* [18], 546 patients with residual tumors less than 2 cm in diameter after initial surgery received adjuvant chemotherapy with cisplatin administered either ip or iv (and 600 mg/m^2 cyclophosphamide iv).

Severe granulocytopenia was 25% more frequent and hearing problems were three times more frequent in the iv group (69% vs 56% and 15% vs 5%).

Abdominal pain is a classical complication of chemotherapy administered by the ip route [26, 27]. After we stopped using doxorubicin, we observed no more cases with pain higher than grade 2, and the pain observed was well soothed by paracetamol and prevented in 90% of cases by adding 20 ml of 2% lidocaïne to the infusion fluid.

We used a needle to administer the drugs ip, so we did not observe the complications usually reported with implantable systems: in particular catheter obstruction and septic peritonitis [22, 23].

No patients died from complications of chemotherapy.

Surgical evaluation at ISCR following neo-adjuvant chemotherapy showed six cases of complete remission, proved histologically and cytologically (46%).

Five (38.5%) of the seven patients in incomplete remission (53%) had residual tumors, few in number and less than 2 cm in diameter, which we were able to remove completely.

Of the two patients with residual lesions more than 2 cm in diameter, one was unable to undergo complete debulking.

These results cannot be compared with published results because we have found no other neo-adjuvant ip trials. Comparisons can only be made with trials of neo-adjuvant chemotherapy administered by the iv route.

In the study reported by Van der Burg *et al.* [19], 278 patients with residual lesions of more than 1 cm in diameter after initial surgery were randomized for further surgery or no further surgery after 3 courses of chemotherapy. Of the 127 patients reoperated, 22 (17.3%) were in complete pathological remission, and of the 105 patients in incomplete remission, 26 (24.76%) were able to undergo ISCR.

These results demonstrate that neo-adjuvant chemotherapy clearly improves the chances of the patients to undergo successful secondary cytoreduction.

Nevertheless, in this study (unlike to our study in which we only performed biopsies) there was some initial debulking to various extents, which may well have played a non-negligible role in modulating the susceptibility of the tumor to chemotherapy.

Tumour reduction, according to Hacker [1, 2], should increase the positive effects of chemotherapy.

The median overall and disease-free survival of our 13 initially inoperable stage IIIc patients, after neo-adjuvant ip chemotherapy followed by ISCR, were 57 and 32 months, respectively.

These results are better than those obtained with iv neo-adjuvant chemotherapy followed by ISCR.

In the study reported by Van der Burg *et al.* [19], the median survival time was 26 months for the patients who underwent further surgery and 20 months for those who did not ($p<0.01$).

Of the 226 patients in Vergote's study [21], 55% underwent initial cytoreduction, and 45% 3 cycles of chemotherapy before ISCR. At three years, the actuarial survival rate of these patients were 26 and 48% ($p<0.0001$), respectively.

Ansquer [20], reported preliminary results for a series of 58 patients inoperable at first intention, 72% of whom after 3 to 6 courses of chemotherapy (mean 4.3) were able to undergo optimal debulking. Median survival time was 21.9 months.

The ip route is little used. Alberts *et al.* [18], showed that first-line cisplatin treatment was more effective than iv cisplatin with a benefit in survival of 8 months and a 24% lower risk of death, but his has failed to change the treatment practice.

Our study shows that ip neo-adjuvant chemotherapy is effective against large tumour load, which should, according to the literature, contra-indicate ip treatment.

We had already observed that neo-adjuvant ip cisplatin-based chemotherapy reduced, and in some cases, eradicated bulky tumors.

Other authors have made similar observations, notably Howell *et al.* in 1990 [28] who, with first-line treatment with a cisplatin-etoposid combination, achieved 68% projected survival at 27 months in 33 stage III-IV patients, after incomplete debulking.

Our treatment was clearly effective as there was no previous chemotherapy; we were able to double the dose of cisplatin and to triple the overall dose, thanks to the use of sodium thiosulfate. DGZ, the biological response modifier (BRM) used, may also have had an effect as an ajduvant of chemotherapy [24, 25]. Other BRM, such as interferon for example, have been reported to be effective [29].

The date of ICSR has been and still is a problem.

The 13 patients consented to ISCR, but given the lack of available information, the number of chemotherapy courses was defined according to tumoral reduction, determined by physical examination, results of imaging and normalization of CA 125. Patients underwent surgery earlier if the results showed consistent improvement and conversely, there were more courses of chemotherapy if the results appeared poor. In our opinion, 4 courses is the minimum for a treatment (mean 4.3 in Ansquer's study [20]) but cytoreduction should be performed as soon as the results of chemotherapy tail off and especially if CA 125 does not decrease or may even increase.

The results of this trial should be interpreted with caution because this is a retrospective study, with a small number of patients, heterogeneous protocols and the number of preoperative courses differed among patients due to the lack of criteria for operability. However, our results are encouraging, particularly as our patients were followed-up for more than 56 months.

Conclusion

The results of this study require confirmation in more extensive trials. We found, with a long follow-up period, that ip chemotherapy administered neo-adjuvantly, contrary to repeated claims in the literature, was effective on bulky tumors.

We observed complete remission in 6 cases of 13, and in all other cases very large tumoral reductions were observed which facilitated secondary cytoreduction.

The survival of the 13 stage IIIc patients can be compared favorably to that obtained with neo-adjuvant chemotherapy administered by the iv route. It would perhaps be of interest in future, to begin at advanced stages with laparoscopy, to evaluate the possibility of resection and to avoid highly hazardous surgery [20].

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Address reprint requests to:
B. ZYLBERBERG M.D.
94 Rue Haxo
75020 Paris (France)