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Sequential Cisplatin–Doxorubicin, Early Debulking Surgery and Intraperitoneal Chemotherapy in Advanced Ovarian Cancer

Aimery de Gramont, Bénédicte Demuynck, Charles Varette, Christophe Louvet, Alain Pigne, Loïc Marpeau, Bertrand Lagadec, Jean Cady, Jean-Yves Couturier, Serge Delfau, Alain Sezeur, Denis Gallot, Michel Malafosse, Jacques Barrat, Marcel Krulik for Groupe d'Etude et de Recherche sur les Cancers de l'Ovaire et Digestifs (GERCOD)

40 patients with advanced ovarian cancer were treated with immediate debulking followed by sequential cisplatin and doxorubicin every 4 weeks, followed by second-look laparotomy (SLL). Six courses were given when residual disease (RD) was under 2 cm. When RD was over 2 cm, three courses were followed by early debulking and six more courses before SLL. Immediate debulking was optimal in 15 patients (38%) and early debulking in an additional 15 (38%). Pathological complete responses (34 evaluable cases) were observed in 14 cases (41%), partial response in 13 (38%), stable disease in 3 (9%) and progression in 5 (15%). Toxicity was mainly haematological. 11 patients with negative SLL and 15 with RD under 2 cm received intraperitoneal cisplatin 200 mg/m² alone or with cytarabine. Median survival was 45 months: 58 months for RD under 2 cm at initial laparotomy and 31 months for RD over 2 cm. Median survival was 46 months when early debulking was successful. 5 year disease-free survival was only 16%. However, this multimodal treatment offers prolonged survival, especially in patients optimally debulked either at initial laparotomy or at early debulking surgery.
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INTRODUCTION

OPTIMAL DEBULKING surgery followed by cisplatin-based chemotherapy is the standard treatment for advanced ovarian cancer. However, immediate debulking is optimal in less than 50% patients and residual disease (RD) over 2 cm in diameter is the worst prognostic factor [1]. Standard combined regimens such as cisplatin/doxorubicin, cisplatin/cyclophosphamide and carboplatin/cyclophosphamide obtain complete tumour response in 20% to 30% of the patients [2]. This corresponds to median survival in the region of 24 months. In a previous series of 48 patients we obtained optimal debulking in 39%, complete responses (CR) with cisplatin/doxorubicin in 23% and a median survival of 22 months [3].

Between 30% and 50% complete responders postchemotherapy ultimately relapsed [4]. We found only 48% 5-year survival after negative second-look laparotomy (SLL) in a series of 32 patients with stage III/IV ovarian epithelial cancer [5].

At the start of our study, early results of promising studies were available. Parker *et al.* reported longer survival after early debulking in patients given short courses of chemotherapy after initial laparotomy leaving bulky residual disease [6]. Bruckner *et al.* showed increased response using the CHAPII regimen partially based on sequential administration of cisplatin and doxorubicin [7]. Intraperitoneal chemotherapy with high-dose cisplatin constituted effective second-line treatment for patients with limited RD [8, 9].

This study attempted to improve survival by introducing sequential cisplatin/doxorubicin at optimal doses, early secondary debulking surgery in patients with residual disease > 2 cm at first laparotomy, followed by high-dose intraperitoneal cisplatin where SLL was either negative or revealed RD < 2 cm.

PATIENTS AND METHODS

From January 1984 to March 1987, 72 patients were referred for advanced epithelial ovarian cancer. 40 of these patients fulfilled the following entrance criteria: age if under 70, FIGO stage III or IV, performance status 0–3, no previous history of invasive cancer, normal heart and renal function, positive follow-up feasibility and informed consent.

Treatment began with surgical debulking while subsequent therapy depended on RD. Optimally debulked patients (RD < 2 cm) received 6 monthly courses of chemotherapy, whereas patients with RD > 2 cm were given three courses of chemotherapy followed by a second laparotomy for maximum additional debulking (early debulking) and six more courses of chemotherapy unless disease was considered progressive.

Chemotherapy consisted of cisplatin 80 mg/m^2 on day 1. Patients received 1 litre of isotonic saline and mannitol 12.5 g before cisplatin administration and 2 l of saline thereafter. Antiemetics were also administered. Doxorubicin 50 mg/m^2 was given intravenously on day 3. Cycles were repeated every 28 days. Chemotherapy was administered where white blood cells (WBC) > 3000/mm^3, platelets > 120,000/mm^3 and serum creatinine < 15 mg/l. Cyclophosphamide 500 mg/m^2 intravenously on day 3 was given from the second cycle onwards if nadir neutrophils were > 1000/mm^3.

SLL was performed after intravenous chemotherapy in patients considered as clinically disease-free by physical examination, including normal chest X-ray and normal abdominal and pelvic echograms or scans.

SLL procedure consisted of median laparotomy, biopsies of any suspect lesions, or systematic multiple biopsies of the peritoneum and peritoneal washings where no RD was visible.

Negative SLL was defined as the absence of residual disease, as confimed by negative biopsies and peritoneal washings. Complete response (CR) was defined as a negative SLL in patients with residual disease at first laparotomy. Partial response (PR) was defined as a decrease of > 50% in the sum of the products of the diameters of measurable lesions. Stable disease was defined as change ranging from < 50% decrease to < 25% increase, and progressive disease covered > 25% increases in RD.

Patients with progressive disease or with RD > 2 cm at SLL were continued on intravenous second-line chemotherapy.

When RD was 0–2 cm at SLL, a peritoneal catheter was installed and the patient was scheduled for intraperitoneal chemotherapy. Drugs were administered in 2 l of saline 7 to 14 days after SLL. The drug-containing isotonic saline was administered by gravity from > 2 m above the patient for high flow rates. Intraperitoneal chemotherapy consisted of cisplatin 200 mg/m^2 alone or in combination with cytarabine 2 g every 4 weeks as per Howell and Markman [9, 10] accompanied by an intravenous bolus of mannitol 12.5 g and thiosulphate 4 g/m^2 in sterilised water. Patients then received intravenous mannitol 30 g and thiosulphate 12 g/m^2 for 6 h. Antiemetics were also given. The peritoneal cavity was drained after 4 h dwelling time and catheters were heparinised. Intravenous fluid therapy was continued for > 24 h. Three courses of intraperitoneal chemotherapy were given to patients with CR at SLL, and six courses if RD was found. Intraperitoneal chemotherapy was administered where WBC > 3000/mm^3, platelet count > 120 000/mm^3 and serum creatinine < 15 mg/l. In January 1986 all patients were put on cisplatin/cytarabine and kept on it if tolerance was satisfactory. However, we discontinued this combined therapy in November 1986 due to absence of obvious benefit over cisplatin alone [11].

Patients with progressive disease, chronic renal failure or positive peritoneal cytology under intraperitoneal cisplatin treatment were switched to IP mitoxantrone 25 mg/m^2 in 2 l of saline.

Subsequent evaluation included physical examination, chest X-rays, abdominal and pelvic computed tomography (CT) and CA-125 dosage every 3 months.

Relapsing patients were first treated with intravenous cisplatin or carboplatin-based combination therapy, followed by high-dose leucovorin and 5-fluorouracil. Figure 1 summarises treatment.

Statistics

The baseline for survival was the date of first laparotomy. The Kaplan–Meier method was used. Logrank tests served to search for prognostic factors. Median follow-up time was 62 months in March 1991.

RESULTS

Patients

Table 1 provides the main data for the 40 patients. Immediate debulking yielded 15 (38%) optimally-debulked patients (RD < 2 cm). Bulky residual disease subsisted in 25 (63%) patients.

Early debulking surgery and evaluation of three first courses of chemotherapy in patients with residual tumour > 2 cm

Early debulking surgery was performed in 21 patients. 4 others with RD > 2 cm were not eligible: 2 stage IV patients showed persistant extra-abdominal disease and two stage III patients developed progressive disease.

Three courses of intravenous chemotherapy obtained CR in 1 patient (5%) and partial response in 16 (76%), while disease proved stable in 2 patients (9.5%) and progressive in 2 others (9.5%).

Correspondence to A. de Gramont, Service de Médecine Interne – Oncologie, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France.
The authors are at the Hôpital Saint-Antoine, Paris, France.
GERCOD members: J. Debray, B. Demuynck, G. Gonzalez-Canali, A. de Gramont, M. Krulik, J.P Loiseau, C. Louvet, J. Seroka, C. Varette, J. Cabane, J. Barrat, T. Jault, X. Guettier, L. Larue, L. Marpeau, O. Chazouillères, R. Poupon, B. Nordlinger, Hôpital Saint-Antoine, Paris; J.D Grangé, F. Bodin, Hôpital Tenon, Paris; A. Pigné, D. Gallot, M. Malafosse, A. Sezeur, Hôpital Rothschild, Paris; D. Zylberait, Hôpital de Compiègne; D. Goujard, Hôpital de Montfermeil; E. Navarro-Carola, Hôpital de Mantes; C. Dray, Hôpital du Perpétuel Secours; F. Krainik, Hôpital Léopold Bellan; Mme Jacomy, Hôpital de Laval; J. Bartholeyns, B. David, CNTS; G. Conscience, Capelle, CMC Porte de Choisy; J.Y. Couturier, J.E Maisani, D. Soubrane, Clinique Floréal, Bagnolet; J. Cady, Clinique Geoffroy Saint-Hilaire, Paris; B. Lagadec, Clinique Bizet, Paris; S. Delfau, Clinique Hoffman, Rosny; Sala, Clinique la Régence, Maisons-Alfort; A. Berken, Stony Brook, New York; Y. Drolet, A. Lavoie, C. Tessier, P. Ouellet, D. Marceau, M. Belanger, Hôtel-Dieu de Québec, Canada; E. Rioux, C. Shields, M. Bergeron, Hôpital Enfant-Jésus, Québec, Canada; I. Karaitianos, P. Vassilopoulos, I. Karayiannis, Hellenic Anticancer Hospital Saint-Louis, Athens, Greece; I. Karamanolis, Hôpital Zannion, Le Piré, Greece.
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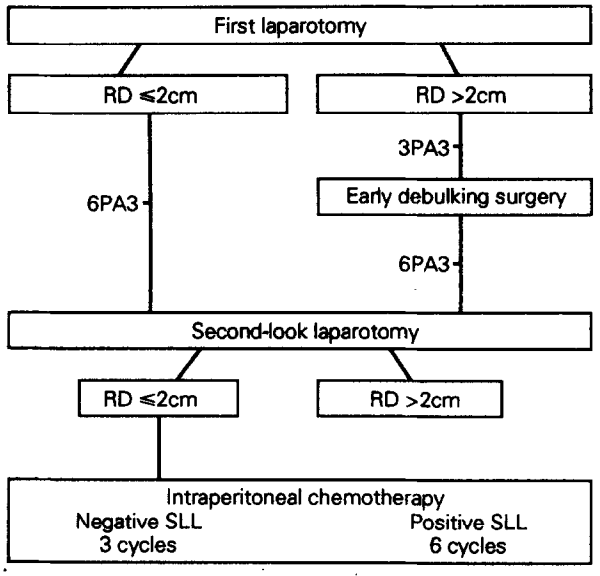

Fig. 1. Treatment in advanced ovarian cancer. RD = residual disease; PA3 = sequential cisplatin–doxorubicin; SLL = second-look laparotomy.

After debulking, no disease was visible in 5 patients, RD < 2 cm was present in 10 patients and 6 showed RD > 2 cm. Early secondary debulking was optimal in 60% (15/25) of patients with bulky RD at first laparotomy (71% of eligible patients, 15/21).

SLL and evaluation of sequential cisplatin/doxorubicin

SLL was performed in 32 patients but not on 8, i.e. 4 patients with progressive disease, 2 patients descheduled due to intravenous chemotherapy toxicity, 1 patient in CR after early debulking surgery, and 1 patient who died early of pulmonary embolism.

Chemotherapy was not evaluable in 6 patients due to 1 early death, 3 cases with no RD after first laparotomy and 2 patients de-scheduled for SLL because of toxicity. However 1 of the 3 patients with no RD had persistent positive cytology and SLL was negative for 2 others. Toxicity developed in 1 clinical CR and 1 partial responder.

CR was observed in 14 patients (41%) and partial response in 13 (38%), while disease proved stable in 3 (9%) and progressive in 5 (15%). For patients with initial RD < 2 cm, 5 were in CR (50%), as compared with CR for 9 patients (41%) whose initial RD > 2 cm. Table 2 summarises response in function of RD at first laparotomy.

Table 1. Patients' characteristics

Age (yr)	
Mean (S.D.)	54.1 (11.7)
Range	22–69
WHO performance status	
0	16
1	17
2	4
3	3
FIGO stage	
III	35
IV	5
RD after initial laparotomy	
None	3
< 2 cm	12
> 2 cm	25
Histology	
Serous	26
Endometrioid	3
Undifferentiated	6
Other	5

Table 2. Tumour response

Stage	Response: Complete	Partial	Stable	Progression	Not evaluable
III Microscopic residual disease					3
III Residual disease ≤ 2 cm	5 (50%)	4	1		
III Residual disease > 2 cm	9 (41%)	7	1	5	1
IV		2	1		2
Total	14 (41%)	13 (38%)	3 (9%)	5 (15%)	

Toxicity of sequential cisplatin/doxorubicin

Haematological toxicity is shown in Table 3. Nausea and vomiting occurred in 37 patients (93%) and grade 3 alopecia in 39 (98%). Febrile neutropenia developed in 4 patients (10%), grade 1 or 2 paresthaesia in 5 (13%), grade 2 mucositis in 2 (5%), as well as 1 case each of reversible renal failure, cardiac arrhythmia and partial deafness.

34 patients were treated at full dose, but doses were reduced for 5. 2 of the 6 patients receiving cyclophosphamide were given more than two courses.

Intraperitoneal chemotherapy

Intraperitoneal chemotherapy was given to 26 out of 29 patients with intraperitoneal RD < 2 cm at SLL. 2 patients refused intraperitoneal therapy and retroperitoneal disease ruled out the intraperitoneal route in a third patient.

Table 3. Haematological toxicity (WHO scale)

	Grade: 0	1	2	3	4
Haemoglobin	17%	52%	9%	22%	0
Neutrophils	0	5%	18%	36%	41%
Platelets	84%	5%	8%	0	3%

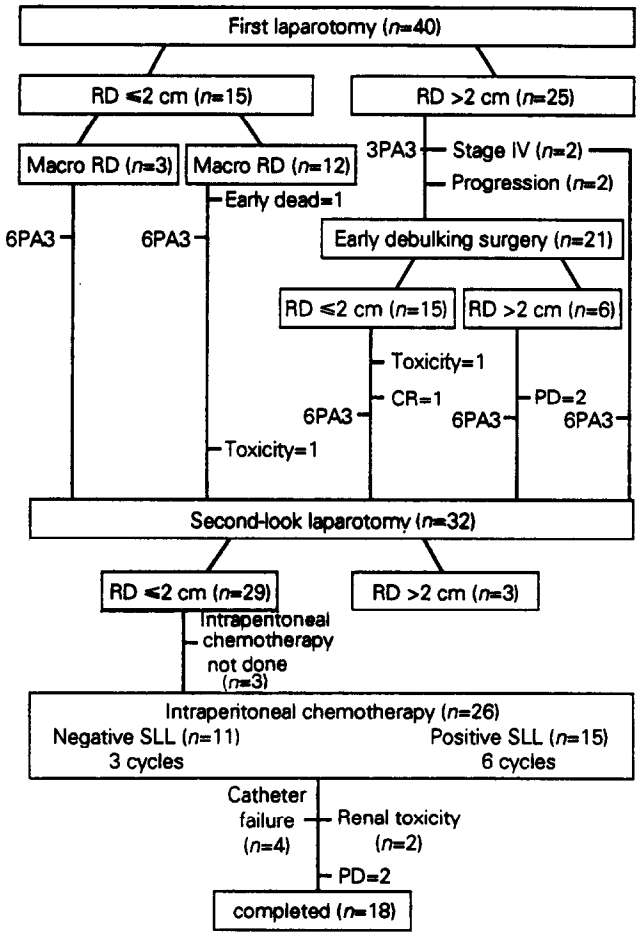

Fig. 2. Treatment outcome in all patients. RD = residual disease; micro = microscopic; macro = macroscopic; PA3 = sequential cisplatin–doxorubicin; CR = complete pathological response; PD = progressive disease.

Catheter complications prevented 4 patients from receiving all cycles of therapy scheduled (3 cases of inflow obstruction and 1 of rectal perforation). 2 patients received melphalan intraperitoneal due to protocol violation. Details of intraperitoneal chemotherapy are given elsewhere [12]. 15 patients received only cisplatin and 9 at least one course of cisplatin with cytarabine. Toxicities were: nausea/vomiting in 24 patients (100%), renal failure in 7 (29%), chronic renal failure in 1 (4%), paresthesia grade 1 or 2 in 6 (25%), abdominal pain in 6 (25%), anaemia requiring transfusion in 3 (12%), leucocyte and platelet toxicity in 5 (21%) with platelets grade 4 in 1 case (4%), deafness in 2 (8%), as well as fever and diarrhoea in 1 patient each (4%). Cisplatin doses were reduced for 3 patients (12%) and cisplatin-based chemotherapy had to be discontinued to 2 patients (8%) due to renal toxicity. 4 patients were extended on intraperitoneal mitoxantrone after two or three courses of cisplatin, 2 because of renal toxicity and 2 others because of positive peritoneal cytology. Treatment outcome in all patients is summarised in Fig. 2.

Survival

Survival is shown in Fig. 3. Median survival for all stage III patients with RD < 2 cm was 58 months, as against 31 months for stage III with RD > 2 cm. 11 patients were still alive in November 1991 (28%). 5-year survival was 32% (S.D. 40–23%) in all patients, 49% (65–34%) for stage III patients with RD

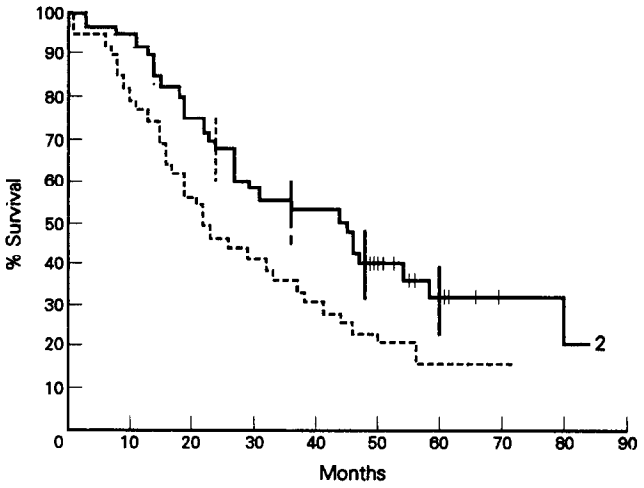

Fig. 3. Survival (——) and progression-free survival (- - - -) in advanced ovarian cancer (large vertical lines = S.D.).

< 2 cm but 24% (34–14%) if stage III with RD > 2 cm. (Fig. 4). The difference in survival between RD < 2 cm and RD > 2 cm ($P = 0.05$) is statistically significant. Median survival for stage III with RD > 2 cm who were optimally debulked after early debulking surgery was 46 months, which was not different to survival for patients immediately debulked.

Disease-free survival (DFS) is shown in Fig. 3. Median overall DFS was 22 months. 16% of patients remained disease-free at 5 years (S.D. 26–13%).

10 patients relapsed or developed progressive disease within 1 year, 11 in the second year, and 5 in the third year. Late progression or relapse were observed at 37, 40, 43, 45, 49 and 56 months. 7 patients remained disease-free at the close of the study and the last patient died early.

Complete responders at SLL had a 67% probability of 5-year survival. Partial responders had 3- and 5-year survival rates of 59% and 29%, respectively (median 45 months). The difference between CR and partial response is not significant. For patients

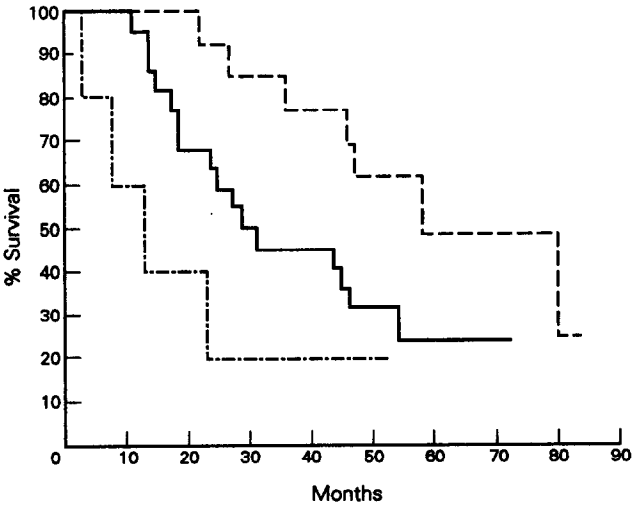

Fig. 4. Survival according to residual disease at first laparotomy. - - - - = stage III, residual mass < 2 cm; —— = stage III, residual mass > 2 cm; - · - · = stage IV.

with progressive disease, 2-year survival was 20% and fell to 4% at 3 years (median 8 months).

DISCUSSION

Median survival > 40 months is rarely reported for advanced ovarian cancer [13–15]. Standard debulking and cisplatin-based combinations obtain median survival ranging from 11 to 36 months [16].

This series of patients achieved 45 months median survival, an improvement over our previous similar series which obtained 22 months median survival. Our findings based on RD are similar: median survival was 58 months compared with 45 months in stage III patients with minimal RD, 31 versus 24 months with RD over 2 cm [3].

Residual tumour size is considered a major prognostic factor. Recent phase III series of patients with RD < 2 cm yielded median survival from 31 to 39 months [17] and 40 months [18]. Bulky RD correlates with 13–20 months median survival [14, 18, 19] and 9% to 26% 5-year survival [21].

Debulking contributes heavily to improved survival although feasible in < 50% patients [14, 18] with the standard procedure. However, Piver *et al.* reported that immediate aggressive debulking brought 87% residual disease down to < 2 cm, which might explain the excellent median survival they obtained (48 months) [13].

We debulked optimally no more than 38% patients at first laparotomy but another 38% patients benefitted from early secondary debulking after 3 courses of chemotherapy (75% total). In principle, the advantage of immediate debulking is that it involves only one laparotomy, while early secondary debulking is either less aggressive, or at least easier due to chemotherapy.

Sequential cisplatin/doxorubicin is derived from the CHAPII regimen developed by Bruckner *et al.* which has given a median survival of 43 months [15]. The rationale for CHAPII is based on *in vitro* experiments showing that sequential administration increases sensitivity to both drugs. Cisplatin is given 24–36 h before doxorubicin [22]. However, our doses of cisplatin were higher than provided for in the CHAPII regimen and we decided to avoid hexamethylmelamine. Our understanding of the literature and previous experience with the standard regimen suggest that the number of drugs was less important than optimal dosage of the two most potent drugs. We obtained 41% pathological CR, compared with 26% using our previous simultaneous cisplatin/doxorubicin regimen. This suggests that sequential cisplatin/doxorubicin is more effective and contributes to improved survival.

Our results also suggest that chemotherapy reaches peak response during the first three courses and that, in the absence of debulking, there is little benefit to be gained from any further initial chemotherapy.

The intraperitoneal route delivers far higher local concentrations of drugs in the peritoneal cavity than in plasma. High-dose cisplatin as a single agent or in combination gives 30–50% overall response, including 6–12% CR via the intraperitoneal route, and is even effective against tumours resistant to cisplatin IV [23, 24]. The best responders are patients with RD < 1–2 cm.

Little appears to have been published to date about survival. Howell *et al.* suggest improved survival with an intraperitoneal cisplatin-based regimen [25]. Cisplatin and cisplatin/cytarabine as used in this study obtain 30–40% response [9, 26, 27].

All the patients we treated with intraperitoneal chemotherapy were either in CR or showed minimal RD. Furthermore, they presented no sign of cisplatin resistance. Yet, this regimen generated no unusual benefit: 5 year DFS was 16% and overall survival was 32%, although catheter and drug complications prevented 23% patients from receiving all courses of therapy.

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Treatment of Malignant Melanoma and Renal Cell Carcinoma with Recombinant Human Interleukin-2: Analysis of Cytokine Levels in Sera and Culture Supernatants

Catherine A. McIntyre, Karen Chapman, Steve Reeder, Mark S. Dorreen, Lesley Bruce, Sheila Rodgers, Khizar Hayat, Thiagarajan Schreenivasan, Eamonn Sheridan, Barry W. Hancock and Robert C. Rees

In this study we evaluated the clinical response of 12 patients with malignant melanoma and renal cell carcinoma (RCC) following administration of recombinant human interleukin-2 (rhIL-2) by continuous infusion. Serum samples taken before, during and following sequential courses of IL-2 were assayed for the presence of tumour necrosis factor alpha (TNF-α) IL-1α, IL-6 and interferon gamma (IFN-γ) and the presence or changes in these cytokines were examined with respect to clinical response data: our results did not show any direct correlation between the parameters measured and clinical outcome. In addition, peripheral blood mononuclear cells (PBMC) derived from 3 RCC patients were cultured in a serum-free environment and the resulting supernatants assayed for the production of these cytokines and compared to the corresponding serum levels. During one or more courses of treatment only 1 patient, who had metastatic bone disease, demonstrated detectable serum TNF-α; serum IL-6 levels were elevated in a proportion of all patients studied and a sustained IL-6 response occurred in a patient who had complete disease remission; IL-1α was detected in the serum of 3 RCC patients; IFN-γ could not be detected in any serum sample tested. Cytokine levels in sera and supernatants derived from 3 RCC patients were compared but no correlation was found: TNF-α and IL-6 were shown to be present at much higher concentrations in supernatants when compared to sera whereas the levels of IL-1α were almost undetectable. This lack of correlation is probably due to the presence of "interfering" proteins in sera which either depress or enhance the ability to detect cytokines in sera using enzyme immunoassays.
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INTRODUCTION

INTERLEUKIN-2 (IL-2) promotes the cytotoxic potential of large granular lymphocytes (LGL) and monocytes [1,2], induces the production and release of cytokines such as interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) [3,4], and is the principle factor required for the induction and growth of lymphokine-activated killer (LAK) cell activity [5]. It is on the basis of these activities and results from preclinical therapy experiments [6] that clinical trials are now being conducted to evaluate the potential of IL-2 as a therapeutic agent in the treatment of human malignant disease: the results of initial studies indicate that a 20–30% clinical response rate can be achieved with some human tumours [7–11].

The mechanism by which some patients with renal cell carcinoma or malignant melanoma respond to recombinant human IL-2 (rhIL-2) therapy is not understood and is the subject of debate and controversy. IL-2 is known not to exert a direct antitumour effect on solid malignancies, and tumour regression, in part, may be a consequence of direct or indirect activation of major histocompatibility complex (MHC)-restric-