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Acknowledgement—This study was supported by the Michaelsen Foundation, the Danish AIDS foundation, the Danish Medical Research Council and the EEC (European Federation of AIDS Research).

Eur J Cancer, Vol. 27, No. 11, pp. 1423–1429, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Treatment of Malignant Ascites due to Recurrent/Refractory Ovarian Cancer: the Use of Interferon-α or Interferon-α Plus Chemotherapy *in vivo* and *in vitro*

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Intraperitoneal treatment with interferon (IFN) for malignant ascites due to advanced ovarian carcinoma refractory to chemotherapy gave an objective response rate of 36% (7/19 patients treated). *In vitro* studies demonstrated that cytotoxicity of peripheral blood monocytes/macrophages was stimulated by IFN. However, peritoneal exudate cells obtained after intraperitoneal treatment with interferon were not stimulated to kill autologous tumour cells. Clinical response was therefore most probably due to a direct inhibitory effect of IFN on growth of malignant cells rather than due to an immune modulatory effect. Using a newly established ovarian cancer cell line (UWOV1), synergy between the growth inhibitory/antitumour effects of IFN and cisplatin was demonstrated at clinically achievable concentrations of each agent. IFN plus cisplatin proved to be more effective than intraperitoneal cisplatin alone in control of peritoneal carcinomatosis. The response rate was 5/7 (77%) for combined modality therapy vs. 2/9 (22%) for intraperitoneal chemotherapy alone. Both *in vitro* and *in vivo* studies suggest a role for interperitoneal therapy for control of refractory ascites in ovarian cancer.
Eur J Cancer, Vol. 27, No. 11, pp. 1423–1429, 1991.

INTRODUCTION

WHILE COMBINATION chemotherapy has resulted in significant improvement in the response rate of ovarian cancer [1, 3], local tumour recurrence remains a major problem. Locoregional treatment with intraperitoneal drug instillation for the treatment and/or prophylaxis of this problem has been studied fairly extensively during the last 10 years [4–7]. The rationale for intraperitoneal therapy is based on the observation that drug concentrations at the tumour site (peritoneal cavity) are significantly higher following intraperitoneal instillation than the drug concentrations which can be achieved following systemic administration [8, 9]. Such increased drug concentrations should achieve a higher cell kill and therefore greater clinical efficacy.

However, many patients with recurrent ovarian cancer will already have been exposed to the most useful drugs before intraperitoneal therapy is given. Such prior exposure increases the risk of drug resistance. While dose escalation may be partly effective in overcoming drug resistance, alternative treatment approaches [10–12] need to be developed. A number of preliminary studies have indicated some potential for intraperitoneal interferon (IFN) [13, 14] for the treatment of peritoneal carci-

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Revised 22 May 1991; accepted 3 June 1991.

nomatosis. In view of the predominantly intraperitoneal pattern of recurrence of ovarian cancer and the favourable peritoneal:plasma concentration ratios for both chemotherapeutic agents [15] and for IFN given by this route [12], ovarian cancer may be an ideal model to study the use of such combination treatment.

The aim of the present study was thus to develop a model for the rational use of interferon in combination with chemotherapeutic drugs.

PATIENTS AND METHODS

Clinical studies

The study population consisted of 35 patients with histologically diagnosed ovarian cancer with cytologically confirmed recurrent malignant ascites. To be eligible for the study patients had to have symptomatic ascites which had required aspiration on more than two occasions and which was rapidly recurrent (re-accumulation to an estimated volume of 2 l or more within 4 weeks). All patients had initially been treated by means of surgery followed by at least six cycles of a platinum-based combination (cisplatin + doxorubicin/epirubicin + cyclophosphamide, PAC or PEC). Patients who had a prior complete response to therapy had to have recurrent, cytologically positive acites which was refractory to retreatment with at least two cycles of a platinum-based regimen before being entered into this study. Patients who had a partial response following the initial six cycles of chemotherapy but who were left with residual ascites and/or intraperitoneal tumour masses received either second-line chemotherapy (mitoxantrone 12 mg/m^2 + etoposide 100 mg/^{2} for 3 days) or pelvic irradiation and/or intraperitoneal chemotherapy prior to entry in this study. Further patient details are shown in Tables 1 and 2. To be eligible for the study patients had to have adequate haematological indices defined as haemoglobin > 10 g/dl, white blood cells (WBC) > 3.0 × 10^9/l, platelets > 100 × 10^9/l and adequate renal and hepatic function (creatinine < 200 μmol/l, bilirubin < 20 μmol/l and transaminases < 2 × normal values).

Baseline investigations included history and physical examination, measurement of weight and of abdominal girth, X-ray of the chest and sonography and computed tomography (CT) of the abdomen and pelvis.

Therapy was administered by a single indwelling intraperitoneal catheter (Tenckhoff) which was inserted at minilaparotomy with the tip directed to the pelvis. This catheter was used both for drainage of ascites as well as for instillation of drugs. After insertion of the catheter ascites was drained and baseline cytological examination and microbial culture was undertaken. The first 19 patients included in this investigation were treated in an unrandomised fashion with intraperitoneal IFN only. Subsequently 16 patients (Table 3) have been entered into a randomised controlled study comparing the use of intraperitoneal IFN plus chemotherapy to chemotherapy alone in patients who had not previously had any exposure to intraperitoneal drugs.

After drainage IFN-α_{2b} (Schering-Plough, New Jersey) was introduced into the peritoneal cavity diluted in 200 ml warmed peritoneal dialysis fluid containing KCl and administered over 20–40 min. The initial dose of IFN-α was 5 U/m^2 twice weekly with a progressive dose escalation over 4 weeks to 15 U/m^2 for patients who tolerated treatment. The combined IFN-α plus chemotherapy regimen consisted of 15 U/ml IFN-α as above plus 400 mg/m^2 carboplatin in 500 ml 0.9% NaCl.

Response was assessed by weekly physical examination, weight and girth measurements and measurement of the volume of ascitic fluid drained together with weekly cytological examination as well as monthly X-rays, sonograms and 3-monthly CT. Patients whose ascites was controlled had cytological examinations performed by instillation of 200 ml of warmed saline into the peritoneal cavity followed by re-aspiration 30 min later. Malignant cells were identified by morphological criteria. The rate of increase of abdominal girth, the average volume of ascitic fluid drained and the number of malignant cells/ml of fluid were compared with both pretreatment and ongoing measurements of the same parameters for each patient. Complete response was defined as no increase in girth as compared to the measurement achieved after drainage following initial insertion of the catheter as well as < 200 ml/week of ascites plus at least three successive negative cytological examinations. Partial response was when there was control of ascites but persistent positive cytological

Table 1. Patients' details

	n	(%)
Histology		
Serous cystadenocarcinoma	17	(89)
Mucinous cystadenocarcinoma	2	(11)
Initial chemotherapy		
PAC/PEC	13	(68)
Carboplatin + cyclophosphamide	6	(32)
Response to initial chemotherapy		
CR*	10	(52)
PR	6	(32)
PD	3	(16)
Additional therapy prior to intraperitoneal treatment†		
Second-line chemotherapy	14	(74)
Pelvic information	2	(11)
Prior intraperitoneal therapy		
Doxorubicin	2	(11)
Cisplatin	3	(16)
Disease status at entry		
Recurrent disease	16	(84)
Progression on primary treatment	3	(16)
Ascites only	10	(53)
Ascites plus intra-abdominal mass	9	(47)
Cytological findings at entry		
Positive	19	(100)
Performance status (ECOG)		
1	7	(37)
2	12	(63)
Time to recurrence (responding patients) (months)		
Median	11	
Range	5–32	
Age		
Mean	52	
Range	43–66	

* 4 CR pathologically confirmed.

† All patients who had CR (clinical and pathological) and who had recurrent ascites were retreated with at least two cycles of a platinum-containing chemotherapy regimen (either PC or carboplatin + cyclophosphamide).

14 patients who had PR with PAC/PEC but who had residual ascites received two cycles of mitoxantrone + etoposide prior to entry into the study and 2 with residual pelvic masses received pelvic irradiation.

Table 2. Treatment of malignant ascites with intraperitoneal IFN-α: response according to pretreatment clinical parameters

	Patients responding	
	n	%
Histology		
Serous	6/17	35
Mucinous	1/2	50
Response to prior treatment		
CR	5/10	50
PR	2/6	33
PD	0/3	0
Performance status		
1	3/7	43
2	4/12	33
Age (years)		
< 50	3/8	38
> 50	4/11	36

examinations after peritoneal lavage. Response which was less than partial (MR) was considered to have occurred if there was > 50% reduction in the combined rate of increase of girth and volume of ascites drained.

Toxicity assessment was by means of WHO criteria [16]. Toxicity monitoring was by means of regular blood counts (initially once weekly followed, if < grade 2 haematological toxicity was present, by blood count every 2 weeks) as well as by regular monitoring of renal and hepatic function and microbiological culture of ascitic fluid.

All patients gave informed consent and the study was approved by the Committee for Ethics of Human Research of the University of the Witwatersrand.

Table 3. Treatment with intraperitoneal chemotherapy or combined intraperitoneal chemotherapy plus IFN-α

	Chemotherapy	IFN-α + chemotherapy
Histology		
Serous	6	6
Mucinous	2	1
Other	1	0
Initial chemotherapy		
PAC/PEC	6	5
Carboplatin and cyclophosphate	3	2
Response to initial chemotherapy		
CR	1	1
PR	7	4
PD	1	2
Disease status and entry		
Recurrent disease	8	5
Progression on primary treatment	1	2
Ascites only	7	3
Ascites and intra-abdominal mass	2	4
Response to treatment		
CR	0	1
PR	2	4
NR	7	2
Total	9	7

Chemotherapy consisted of carboplatin 600 mg/m², IFN-α 15 U/m². Criteria for patient selection and response were similar to those for patients treated in the initial study with IFN-α alone.

In vitro *investigations*

Cell lines. The UWOV1 cell line used for *in vitro* investigations was established from one of the patients with malignant ascites due to ovarian cancer which had recurred while on treatment with PEC. This cell line has been shown to be of epithelial derivation and has been in continuous culture for more than 3 years. The characteristics of this cell line have been described in a previous publication [17]. The K562 cell line was obtained from the ATCC (American Type Culture Collection Rockville, Maryland) repository and has been maintained at this institution under the optimal growth conditions. K562 cells have previously been shown to be highly sensitive to mononuclear cell-mediated cytotoxicity [18].

Peripheral blood monocytes were obtained from 4 normal volunteers and also from 3 of the patients prior to entry into the study. These 3 included the patient from whose ascites the UWOV1 cell line had been derived. Peripheral blood was drawn by venepuncture into heparinised tubes. Monocytes were isolated by Ficoll–Hypaque density gradient separation, the cell density layer being removed. Further separation was by means of adhesion. Cells were suspended in Hank's buffered salt solution (HBSS) with 5% albumin and were then allowed to adhere to plastic petri dishes for 1 h at room temperature. Non-adherent and loosely adherent cells were removed by washing three times with HBSS and tapping the petri dishes against the laboratory bench for 2 min before pouring off the HBSS and the more loosely adherent cells. Target cells were added to the residual tightly adherent cells for macrophage cytotoxicity studies.

Peritoneal exudate cells were obtained via Tenckhoff catheter 1 week after the first intraperitoneal instillation of IFN-α. For collection of peritoneal exudate cells, residual ascites was drained by gravity. This was followed by instillation of 300 ml warmed HBSS for 30 min. The instilled fluid was then drained, first by gravity drainage followed by aspiration with a syringe where necessary. The collected fluid was centrifuged at 5000 *g* for 20 min at 4°C and the cell pellet resuspended in HBSS. Red cells were lysed by hypotonic shock, the remaining cells were again pelleted, washed and resuspended in HBSS to a final volume of 10 ml.

Counting of peritoneal exudate cells. Aliquots of ascitic fluid and peritoneal washings were counted in a hemocytometer chamber for total cell counts. Differential counts were performed on cytospin preparations which were stained with Papanicolaou stain for identification of tumour cells and with a peroxidase stain to assist in identification of monocytes. Lymphocytes were identified by morphological features and by immunofluorescent staining for T-cells (using anti CD-2 fluorescene conjugated monoclonal antibody) and immunofluorescent antibody staining for kappa and lambda light chains (for B-cell identification). The numbers of reactive peritoneal exudate cells were calculated from the total cell count minus the proportion of morphologically identifiable tumour cells as well as by calculating the number of cells identified as monocytes and lymphocytes (T-cells and B-cells) and expressing these as a proportion of the total cell

count. Good correlations were obtained between the estimates of reactive cells vs. malignant as determined by these two methods.

Monocyte cytotoxicity. Monocyte cytotoxicity was assessed by the ^{51}Cr release assay [19]. Target cells were labelled with 5.55 MBq Na $^{51}CrO_4$ (Amersham International, Buckinghamshire, UK) for 45 min at 37°C. The cells were then washed three times in HBSS and resuspended in tissue culture media. Peripheral blood monocytes or peritoneal exudate cells were added at various effector: target ratios in control experiments or in experiments in which monocytes had been pretreated with IFN for up to 24 h prior to addition to target cells. Cytotoxicity was determined over a 4 h period at 37°C in 96 well microtitre plates. Percentage chromium release was calculated after subtraction for spontaneous release of label: $(a - b) \times 100 \div c$, where a = cpm released in the presence of effectors, b = cpm released without effectors and c = total cpm incorporated.

Cytotoxicity of chemotherapeutic agents against UWOV1 in the presence and absence of IFN. Sensitivity of UWOV1 to a variety of chemotherapeutic agents was tested in the presence and absence of IFN-α. Cytotoxicity was tested both by assessment of percent viability after incubation with chemotherapeutic agents for 1 h and by estimation of cell growth following either short (1 h) or prolonged (72 h) exposure of cells to chemotherapeutic agents. Growth experiments were performed using an initial cell density of 5×10^5 cells per well in multiwell plates in KSLMS media plus 5% fetal calf serum as previously described [17]. For short (1 h) exposures, cells were suspended in media and drug and then washed three times in HBSS prior to plating. For 72 h exposures cells were plated directly into drug-containing media. Growth medium was changed to non-drug-containing medium after 72 h. Cell growth was assessed by performing cell counts and comparing growth curves of treated cells to control experiments with cells not exposed to drugs. Cultures were continued for up to 7 days. Cell counts were performed at 72, 120 and 168 h. All experiments were performed in triplicate with cells derived from stocks from passages 32–36. Growth curves for controls agreed to within < 7%. Results were expressed as percentage inhibition of cell growth according to the formula:

$$100 - \left(\frac{\text{cell number after drug exposure}}{\text{cell number control}} \times 100\right).$$

The drug concentrations chosen for study included clinically achievable plasma concentrations within a 1 log concentration range.

For experiments where IFN-α was used in combination with cisplatin, cells were exposed simultaneously to both agents.

Table 4. Treatment of malignant ascites with intraperitoneal IFN

	Ascites only	Ascites plus masses
CR	3	0
PR	4	0
MR	1	1
NR	2	8
Total	10	9

$\chi^2 = 6.8, P < 0.05$.
CR = control of ascites (< 200 ml fluid per week) negative cytology, PR = control of ascites, persistent or intermittently positive cytology, MR = > 50% reduction of weekly volume of ascites drained but persistently > 200 ml/week.

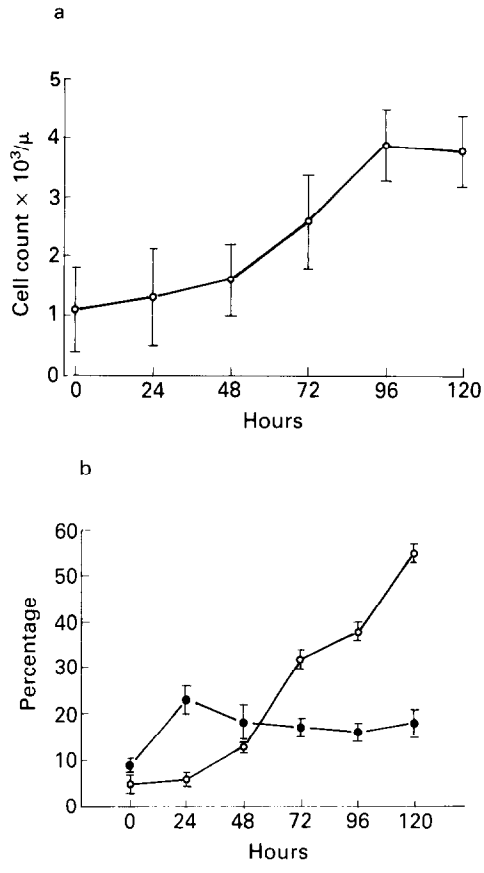


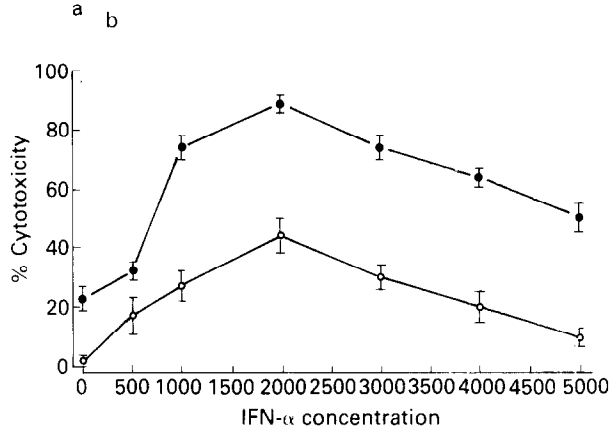
Fig. 1. Cellular reaction after intraperitoneal instillation of IFN-α. (a) Total cell counts, performed daily in 9 patients after a single dose of IFN-α, 5 U/m²; (b) percentage of lymphocytes and monocytes/macrophages.

RESULTS

Clinical response to intraperitoneal IFN alone is shown in Table 4. 7 of 19 patients showed an objective response to therapy. Duration of response ranged from 3 to 11 months with a median of 5 months. 4 patients again showed progression after initial response to intraperitoneal IFN. All 4 progressed with development of solid mass lesions with no or only minimal recurrence of ascites.

Figures 1a and b show the nature of the cellular reaction following intraperitoneal IFN amongst 9 patients in whom cell counts were monitored daily over a period of 5 days following instillation of 5 U/m² IFN-α. By 48 h after instillation of IFN-α the predominant cell types in the peritoneal exudate were monocytes/macrophages. This mononuclear cell reaction increased progressively during the 5 day observation period. Active phagocytosis (ingestion of heat-killed *C. albicans*) was demonstrated in > over 85% of such mononuclear cells.

In view of these findings, *in vitro* studies of the ability of IFN-α to stimulate monocyte-mediated cytotoxicity were undertaken. Figure 2 shows the pooled results from seven separate experiments which included peripheral blood monocytes from 4 normal volunteer donors and from 3 patients with ovarian cancer



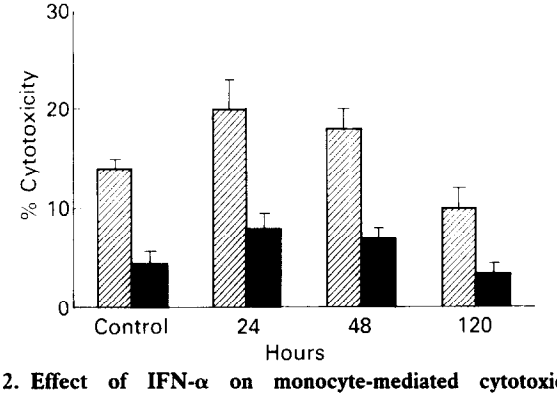


Fig. 2. Effect of IFN-α on monocyte-mediated cytotoxicity. (a) Effector cells: peripheral blood monocytes, target cells: UWOV1 (○) and K562 (●). Effector: target ratio = 50:1. (b) Effector cells: peritoneal exudate cells, target cells: UWOV1 (■) and K562 (▨). Effector: target ratio = 50:1.

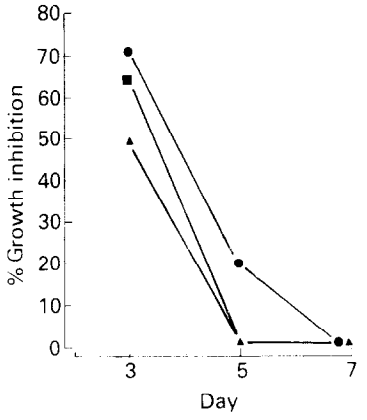


Fig. 3. Effects of IFN-α on growth of UWOV1 cells.

including the individual from whose ascitic tumour one of the target cell lines (UWOV1) was derived.

While the K562 cell line was considerably more sensitive to monocyte killing than UWOV1 the pattern of IFN-stimulated, monocyte induced ^{51}Cr release from both cell lines was similar. The response in both instances appeared to be biphasic with maximal killing achieved at a concentration of IFN-α of 2000 U/ml. However, when the same experiments were repeated using peritoneal exudate cells which had been exposed to IFN-α *in vivo* for 5–7 days, cytotoxicity against target tumour cell lines was not significantly greater than that of control peritoneal exudate cells obtained prior to intraperitoneal installation of IFN-α (Fig. 2b).

The UWOV1 cell line was then used as a model system to test the direct growth inhibitory effects of IFN-α. Figure 3 shows that a short exposure (1 h) to IFN-α prior to plating of UWOV1 cells caused a significant and dose-dependent growth inhibition at day 3 as compared to control cultures. However after such short-term IFN-α exposure, the growth inhibitory effects disappeared rapidly, with cell numbers returning to control levels by day 5 at the lower IFN-α concentrations and by day 7 at the highest concentration tested (3000 U/ml).

Continuous exposure of UWOV1 cells to IFN-α for periods of up to 72 h allowed for more prolonged growth suppression. However, at all IFN-α concentrations tested, up to and including 10 000 U/ml, some cells survived and were able to proliferate again following addition of fresh medium.

The pattern of sensitivity of the UWOV1 cell line to *in vitro* exposure to various chemotherapeutic agents is shown in Fig. 4. Significant resistance (defined as the ability of more than 30% of cells to survive and grow at a concentration 10 times the clinically achievable peak serum concentrations) to a variety of chemotherapeutic agents was demonstrated. This observation accords with the clinical resistance of the *in vivo* tumour of the patient from whom the cell-line was derived to combination chemotherapy.

Figure 5 shows the effects of cisplatin to combination with IFN-α on the growth of the UWOV1 cell line. Although both the degree and duration of growth inhibition of UWOV1 could be increased by increasing the concentration of cisplatin from 2 μmol to 20 μmol, even at the higher dose there was significant recovery of cell growth by day 7 following a single 1 h exposure to drug. The use of cisplatin plus IFN-α appeared, however, to be synergistic (i.e. growth inhibition with the combination when either agent alone at a particular concentration was ineffective). This is demonstrated futher when lower concentrations

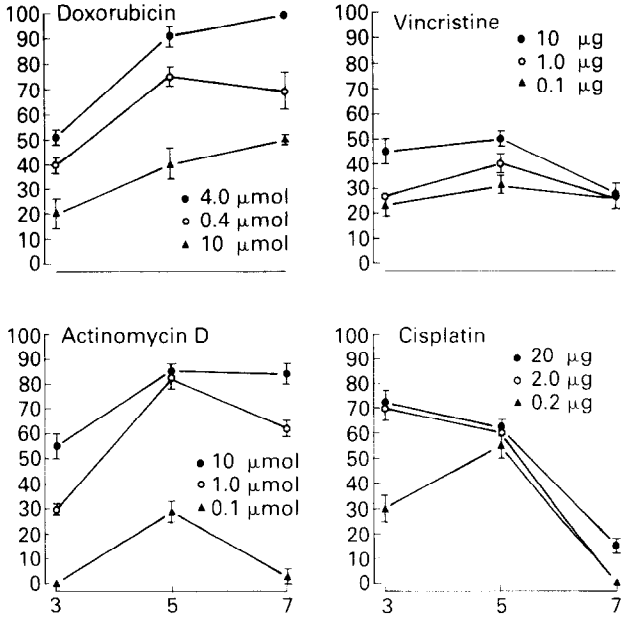


Fig. 4. *In vitro* sensitivity of UWOV1 to chemotherapeutic agents. Exposure to doxorubicin and cisplatin was for 1 h, exposure to vincristine and actiomycin D72 h. Results are expressed as percentage growth inhibition [mean (S.D.)] as compared to controls grown for similar times but without drug exposure.

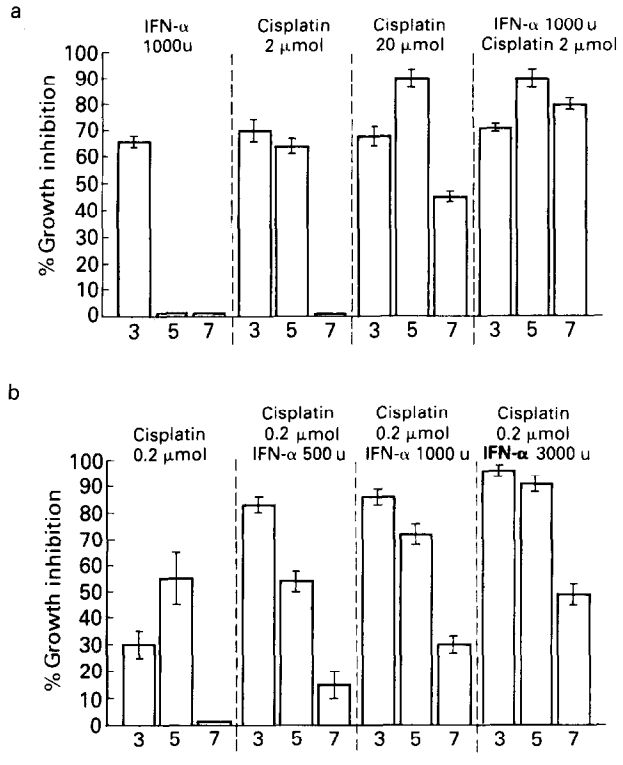


Fig. 5. Effects of IFN-α and IFN-α plus cisplatin on growth of UWOV1 cells. Simultaneous exposure to IFN-α and cisplatin was for 1 h prior to plating.

(0.2 μmol) cisplatin were used together with increasing amounts of IFN-α. In both experiments, growth inhibition was still evident at day 7 when regrowth of cells exposed to only one or the other agent had occurred. Similar results using the combination of IFN-α plus chemotherapy were demonstrated for all drugs shown in Fig. 4 apart from actinomycin D. The most synergistic interaction was, however, with cisplatin.

The results of an ongoing study using intraperitoneal chemotherapy alone vs. intraperitoneal chemotherapy plus IFN-α are shown in Table 5. In the combined modality treatment group, 5/7 (77%) patients showed an objective response to treatment including IFN-α while only 2/9 (22%) patients treated with intraperitoneal chemotherapy alone responded. This difference in response rates was statistically significant ($P < 0.05$). The median duration of response has not yet been reached.

Table 5. Intraperitoneal IFN-α or IFN-α plus chemotherapy for recurrent ascites due to ovarian cancer

	Toxicity	
	Number	Maximum grade
Interferon only		
Chills and fever	6/19	2
Haematological suppression	3/19	2
Peritonitis	4/19	2
Obstruction	2/19	2
Combined therapy		
Chills and fever	4/16	2
Haematological suppression	6/16	2
Abdominal pain	4/16	2
Nausea and vomiting	6/16	3
Peritonitis	2/16	2

Toxicity related to intraperitoneal therapy (Table 5) was mild and was mostly related to complications of intraperitoneal catheters. Systemic toxicity of chemotherapeutic drugs did not appear to be enhanced by the combined use of interferon plus chemotherapy.

DISCUSSION

The treatment of patients with ovarian cancer who have relapsed or progressed after systemic chemotherapy remains unsatisfactory. Such patients are often resistant to further systemic chemotherapy and/or radiation therapy. While the use of intraperitoneal chemotherapy may allow for higher intraperitoneal drug concentration ratios [21, 22] the clinical results achieved so far with this approach do not appear to be effective in eradicating tumour in any substantial number of patients with overt disease. The use of intraperitoneal IFN for treatment of ovarian cancer was first described by Berek and coworkers [10]. Subsequent publications, including one from this unit confirmed significant activity for the use of intraperitoneal IFN in control of malignant ascites in patients with ovarian cancer. The aims of the present study were to extend these observations, to investigate the mechanism of action of intraperitoneal IFN and to develop a rationale for the use of intraperitoneal IFN in combination with chemotherapy.

IFNs are known to have both antiproliferative as well as immune modulatory activities [23–26]. There has been considerable debate in the literature as to which mechanism is responsible for the antitumour effects. Among the immune modulatory effects of IFNs, the one which has received the most attention is their effect on natural killer (NK) cells. In this regard a number of studies have shown enhanced NK cell activity with the use of natural IFNs [27, 28]. However, decreased NK cell activity has also been described [29, 30]. While this apparent variability of NK cell responses has not been fully explained, the differences may be related to the type and source of IFN as well as the dose [31].

Modulation of T-cell functions as well as an increase of monocyte/macrophage dependent cytotoxicity has been also previously described with the use of IFN-γ [32]. The effect of IFN-α on monocyte cytotoxicity has been less extensively investigated. In the present study it was decided to investigate the effects of IFN-α on monocyte/macrophage dependent cytotoxicity in view of the finding that monocytes/macrophages were the predominant reactive cell population following in the peritoneal administration of IFN-α.

Studies with peripheral blood monocytes indeed showed that IFN-α is able to stimulate monocyte cytotoxicity. This enhancement of peripheral blood monocyte cytotoxicity was expresed both against a cell line (K562) known to be sensitive to mononuclear cell cytotoxicity as well as against the new ovarian carcinoma cell-line, UWOV1. The effect of IFN-α on monocyte cytotoxicity appeared to be biphasic with loss of the stimulatory effect at higher doses. Such variability of effector cell responses may be similar to the observations regarding NK cell activity. Thus, if immune modulation were the mechanism of action of the antitumour effect, such dose dependency might have important therapeutic implications. However, the observation that although peripheral blood monocyte cytotoxicity could be stimulated, peritoneal exudate cells failed to show significant cytotoxicity after IFN-α exposure suggests that the major effect of interferon treatment is not due to immune/cytotoxic effector cells.

Direct suppression of tumour cell growth by IFNs has previously been described for a number of tumour cell lines as well as in experimental animal systems [23, 24]. Of interest in the present studies was the opportunity to establish a tumour cell-line which showed growth suppression by IFN-α in *in vitro* studies and to confirm by *in vivo* observations that clinical response of the malignant ascites occurred following intraperitoneal treatment with IFN-α. However, both *in vitro* studies as well as *in vivo* observations showed that escape from IFN-α induced growth suppression eventually occurred.

For this reason it was decided to use this model to test the interaction of IFN-α and chemotherapy.

IFN-α appeared to enhance the cytotoxic/growth suppressive effects of a number of chemotherapeutic agents of different classes against the UWOV1 cell-line. The most synergistic combination, however, appeared to be IFN-α plus platinum. Synergistic effects of IFN-α and cisplatin have previously been described by Inoue and coworkers [33].

Based on the *in vitro* findings, a further clinical study was thus undertaken comparing the use of combined modality treatment to the use of chemotherapy alone. The results of this study appear to confirm the predictions made by the model. While intraperitoneal chemotherapy alone gave a partial response in 2/9 patients (a response rate similar to what would be expected from the result in the published literature for patients with overt disease), a significantly higher response rate was achieved with the combination of intraperitoneal IFN-α plus intraperitoneal chemotherapy. While the numbers of patients is small at this time and the duration of response has not as yet been determined, these results give some hope that the application of combined modality treatment to patients with more favourable, microscopic residual disease may give even better results.

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Acknowledgement—This work was supported by grants from the National Cancer Association (SA) and Bekker Trust Foundation.