Pergamon

European Journal of Cancer Vol. 30A, No. 7, pp. 946–950, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)E0103-B

Carboplatin and α-2b Interferon Intraperitoneal Combination as First-line Treatment of Minimal Residual Ovarian Cancer. A Pilot Study

G. Frasci, A. Tortoriello, G. Facchini, S. Conforti, G. Persico, P. Mastrantonio, A. Cardone and R.V. Iaffaioli

21 untreated ovarian cancer patients with stage III and minimal tumour size, were given weekly intraperitoneal (i.p.) carboplatin (150 mg/m²) and α-2b interferon (IFN) (30 million U/m²) for a total of 12 courses, from June 1989 to February 1993. To date, a total of 248 courses have been administered. Toxicity was seldom severe, although fever (179 courses), fatigue (141 courses) and other IFN-related side-effects were very frequent. No patient refused to continue treatment, but in 5 patients IFN dose had to be reduced, and in 1 it was discontinued. The IFN mean delivered dose intensity was 19.8 million U/m² week. Grade 3–4 myelotoxicity occurred in 7 patients (39 courses), but no deaths related to treatment occurred. The actual mean dose intensity of carboplatin was 121.5 mg/m² week. To date, 20 patients have completed treatment and are evaluable for response. Of 11 patients with tumour size ≤ 5 mm, 10 (91%) achieved a pathological complete response (pCR) as did 4/9 (44%) of those with tumour > 5 mm at entry, for a 70% (95% confidence interval 50–90) overall pCR rate. At a median follow-up of 21 months (range 4–46), only one death occurred. The probability of being alive at almost 4 years was 91% in the entire group (100% in those with tumour size less than 5 mm). Only 1 of 14 patients who achieved a pCR relapsed. This i.p. combination seems a feasible approach to previously untreated ovarian cancer patients with minimal tumour burden. IFN dosage should be reduced to improve tolerance. In view of the very high pCR rate achieved in the group of patients with smaller tumours, a randomised trial is warranted to compare this approach to standard treatment in these patients.

Key words: intraperitoneal immunochemotherapy, α-2b interferon, ovarian cancer, minimal residual disease, carboplatin, dose intensity
Eur J Cancer, Vol. 30A, No. 7, pp. 946–950, 1994

INTRODUCTION

SYSTEMIC CISPLATIN/carboplatin-based chemotherapy often fails to achieve a pathological complete response (pCR) even in ovarian cancer patients with slight tumour burden (< 2 cm) after surgery [1].

Since these drugs have been shown to be effective after intraperitoneal (i.p.) administration in ovarian cancer patients unresponsive to systemic treatment [especially in patients who previously responded to first-line intravenous (i.v.) chemotherapy] [2–7], i.p. cisplatin or carboplatin would seem a reasonable first-line treatment in ovarian cancer patients with minimal residual disease after surgery.

I.p. α-2b interferon (α2b IFN) has also produced a high response rate in patients with residual tumour ≤ 5 mm. Moreover, it appears to potentiate *in vitro* antitumour effects of cisplatin and carboplatin [8–10].

The cisplatin/carboplatin–α2b IFN i.p. combination proved to be well tolerated and reasonably effective in relapsed ovarian cancer patients [11–14].

This paper presents preliminary results of a phase I–II pilot study testing a combination of carboplatin and α2b IFN as first-line treatment in patients with stage III minimal ovarian cancer. We performed short-term weekly treatment on the basis of the high dose intensity and efficacy reported by Mangioni and colleagues [15] after short-term treatment with cisplatin in a weekly schedule. Another reason for the weekly schedule was that it theoretically allows more frequent exposure of tumour cells to the combination of these two drugs. The reason for the shortness of the treatment was that the efficacy of long-term i.p. therapy could be impaired by the formation of wide peritoneal adhesions due to both surgery and chemotherapy. Our purpose was to determine whether this totally i.p. approach could achieve a higher pCR rate and possibly cure rate than standard systemic treatment. Pooled results [16] of trials employing cisplatin-based treatments in this subset of patients suggested a pCR rate of

Correspondence to G. Frasci at Casella Postale 105, 84014 Nocera Inferiore (SA), Italy.
G. Frasci, A. Tortoriello, G. Facchini and R.V. Iaffaioli are at the Cattedra di Oncologia Medica Università di Cagliari, Via S. Giorgio 12, Cagliari; G. Persico is at the Cattedra di Chirurgia Generale II Facoltà di Medicina Napoli, 80131 Napoli; and S. Conforti, P. Mastrantonio and A. Cardone are at the Cattedra di Ginecologia ed Ostetricia Università di Catanzaro, 88100 Catanzaro, Italy.
Revised and accepted 17 Jan. 1994.

approximately 50% in patients with tumour size ≤ 2 cm. Further differences in terms of response rate and survival exist between patients with tumour size smaller versus larger than 5 mm. In view of this, we aimed for at least a 70% true pCR rate in patients with tumour ≤ 5 mm and 50% in the others.

PATIENTS AND METHODS

Patients

Between June 1989 and February 1993, 21 untreated patients with a histologically-confirmed diagnosis of ovarian cancer, and minimal residual disease after surgery (≤ 2 cm), median age 55 years (range 38–71), were considered eligible for entry into this phase I–II trial, after receipt of informed consent and a central pathology review. 5 patients had microscopic tumour, 6 had macroscopic tumour less than 5 mm in diameter and 10 had tumour larger than 5 mm. Further eligibility requirements included age ≤ 75 years, ECOG performance status 0–2 and absence of myocardial, renal, hepatic and neurological impairment. Patients' characteristics are outlined in Table 1.

Treatment plan

Peritoneal access was achieved via a temporary catheter (i.v. cath 18 gauge, Becton Dickinson Co., Rutherford, New Jersey, U.S.A.) blindly inserted into the left iliac region after subcutaneous anesthesia.

All patients underwent abdomino-pelvic computed tomography with peritoneal administration of soluble contrast (in 2000–3000 ml of normal saline) before starting treatment, in order to assess the diffusion of fluids in the peritoneum [17]. Treatment regimen included carboplatin (150 mg/m^2) and α2b IFN (30 million U/m^2) administered together i.p. in 2 l of normal saline at 37°C, weekly for a total of 12 courses. Granulocyte colony stimulating factor (G-CSF) (30 million U/day subcutaneously) was administered in patients showing grade 4 neutropenia until recovery (at least 1000 neutrophils/ml).

Within 1 month of the end of treatment, a second-look laparotomy was planned in patients who had evaluable tumour at entry. The laparotomic procedure consisted of xipho-pubic incision, assessment of the size of macroscopic residual tumour, if present, and its removal (when feasible); multiple biopsies of suspected lesions and of previously involved areas, and random biopsies of the high-risk regions were obtained. Multiple peritoneal washings were performed when no macroscopic tumour was found.

Table 1. Patients' characteristics

No. of patients	21
Age (years)	
Median	57
Range	(39–73)
ECOG performance status	
Median	0
Range	(0–1)
Histology	
Serous	14
Mucinous	2
Mixed	2
Undifferentiated	3
Grading	
I	6
II	8
III	7
Tumour size	
Microscopic	5
≤ 5 mm	6
> 5 mm	10
No. of courses	248

Statistical methods and study design

Recurrence and survival curves were estimated using the Kaplan–Meier method [18].

Since our purpose was to achieve at least a 70% pCR rate in patients with tumour ≤ 5 mm and 50% in the others, we estimated the 95% confidence interval for several sample sizes on the basis of these target percentages. At each level, accrual was stopped if the number of pCRs achieved was lower than minimum (combination rejected) or higher than maximum (combination accepted for larger randomised trials).

We planned a maximum sample size of 35 patients for both groups, since at this level each pCR rate achieved exceeded the 95% confidence intervals of percentages which we considered unacceptable: tumour size ≤ 5 mm percentage rejected 40% [95% confidence interval (CI) 24–56], tumour size > 5 mm percentage rejected 20% (95% CI 7–33) (Table 2).

Toxicity evaluation

Toxicity was assessed as follows: routine laboratory checks and physical examination were performed weekly during treatment. Toxicity was graded according to the WHO drug toxicity scale. We did not reduce doses while white blood cells ≥ 3000/ml and platelets ≥ 100 000/ml or creatinine ≤ 1.4 mg/l. A 50% dose reduction was performed if WBC were 2000–3000/ml, platelets 75 000–100 000/ml, creatinine 1.4–2.0 mg/l. IFN dose was reduced to 10 million U/m^2 if severe fatigue occurred. If more than 4 weeks elapsed after the last course, the patient was excluded from the study.

Response evaluation

We considered three parameters to evaluate patients' outcome: (1) pCR achievement; (2) relapse-free interval; (3) overall survival.

pCR was considered as the absence of macroscopic or microscopic residual tumour at second-look laparotomy.

Partial response was defined as a > 50% reduction in the sum of the main diameters of the tumour nodule.

Stable disease was defined as no appearance of new lesions, and an increase not greater than 25% in the sum of the main diameters of the tumour mass. Progression was defined as the appearance of new lesions or an increase > 25% in the sum of the main diameters of pre-existing nodes.

Table 2. Accrual plan based on the 95% confidence intervals of the target pCR rates

Sample size	Tumour size ≤ 5 mm No. of pCRs (%)	Tumour size > 5 mm No. of pCRs (%)
5 patients	1–5 (30–100)	0–5 (0–100)
10 patients	4–10 (40–100)	2–8 (20–80)
15 patients	7–14 (46–94)	4–12 (24–76)
20 patients	10–18 (50–90)	6–14 (28–72)
25 patients	13–22 (52–88)	7–17 (30–70)
30 patients	16–25 (54–86)	10–20 (32–68)
35 patients	20–30 (57–83)	12–23 (34–66)

Relapse-free survival was measured from the date of pCR achievement to the date of documentation of relapse.

Survival was measured from the date of entry to the time of tumour-related death. Deaths due to intercurrent diseases were considered non-failures.

RESULTS

Toxicity

All patients were evaluable for toxicity for a total of 248 courses (Table 3). No major complications related to the route of administration were registered. Local toxicity was not a major problem. 7 patients experienced abdominal pain, but never severe enough to require narcotic analgesia. Chemical peritonitis and adhesions were found in 5/20 (25%) patients submitted to laparotomy. No allergic symptoms were reported. Fever occurred in 179 (72%) courses, and in 43 was over 39°C. IFN dose was reduced by two thirds in 5 patients because of persistent, severe malaise and fatigue, and in one of these, IFN had to be discontinued. Grade 3–4 myelotoxicity (causing treatment delays) occurred in 7 patients (37 courses), but no sepsis-related deaths occurred. In 5 patients we administered granulocyte colony-stimulating factor (G-CSF) for grade 4 neutropenia. The mean duration of treatment delays was 1.1 weeks. In 29 courses, a 50% dose reduction was made necessary by the occurrence of grade 2 leuco-thrombocytopenia. The mean delivered dose intensity was 121.5 mg/m^2/week for carboplatin and 19.8 million U/m^2/week for IFN. Carboplatin-related emesis was generally mild or moderate (only 2 patients experienced grade $\geq$ 3). Transient nephrotoxicity occurred in 1 patient, and peripheral neuropathy in 3 patients.

Response

To date, 20 patients have completed treatment and are evaluable for response. Of 11 patients with tumour size $\leq$ 5 mm, 10 (91%; 95% CI 74–100) achieved a pCR, as did 4/9 (44%; 95% CI 12–76) of those with larger tumours for a 70% (95% CI 50–90) overall response rate (Table 4). 4 patients presented stable disease and 2 presented progression. Only 2/6 non-responders responded to second-line treatment consisting of a combination of cisplatin, epirubicin and cyclophosphamide. At a median follow-up of 21 months (range 4–46), only one disease-related death was observed. The estimated probability of being alive at almost 4 years was 91% [83–99] (Figure 1) in the entire group (it was 100% in patients with smaller tumour size). Only 1/14 complete responders (with > 5 mm tumour size at entry) relapsed. For complete responders, the estimated probability of being free of relapse at almost 4 years was 86% [73–99] (Figure 2). However, it was 100% in patients with smaller tumours at entry.

Table 3. WHO grade of toxicity in 248 cycles

	WHO grade				
	0	I	II	III	IV
Anaemia	164	39	25	15	5
Leucopenia	119	77	25	20	7
Thrombocytopenia	144	67	27	10	—
Abdominal pain	188	35	25	—	—
Fever	69	77	59	43	—
Headache	154	72	22	—	—
Malaise	126	75	37	10	—
Fatigue	95	72	59	22	—
Renal toxicity	246	2	—	—	—
Emesis	84	89	57	13	5
Neuropathy	216	27	5	—	—

Table 4. Patients according to tumour size with surgically documented response (%)

Response	CR	SD	PD	No. of patients evaluable
Microscopic	5 (100)	—	—	5
≤ 5 mm	5 (83)	1 (17)	—	6
> 5 mm	4 (44)	3 (33)	2 (22)	9
Total	14 (70)	4 (20)	2 (10)	20

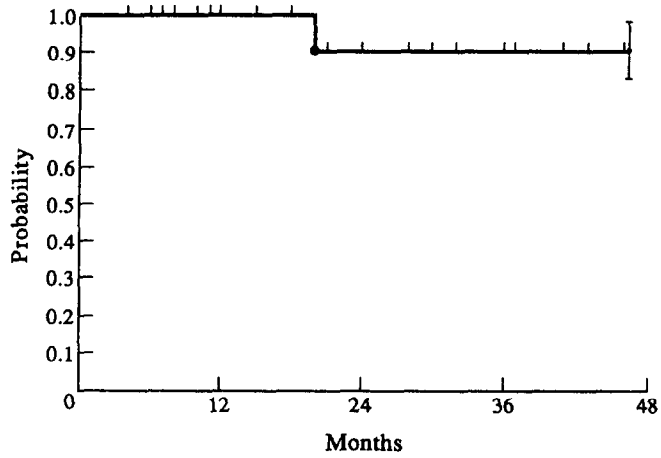

Figure 1. Overall survival

DISCUSSION

Systemic chemotherapy is often unable to effectively eradicate small tumour nodules or even microscopic residual tumour. Intraperitoneal administration may provide a real pharmacokinetic advantage by exposing the intracavity tumour to higher concentrations than those achievable by i.v. infusion [2]. Cisplatin and carboplatin proved to be the most appropriate drugs for i.p. administration, in view of their concentration 10–20 times higher in the peritoneum, good systemic exposure after i.p.

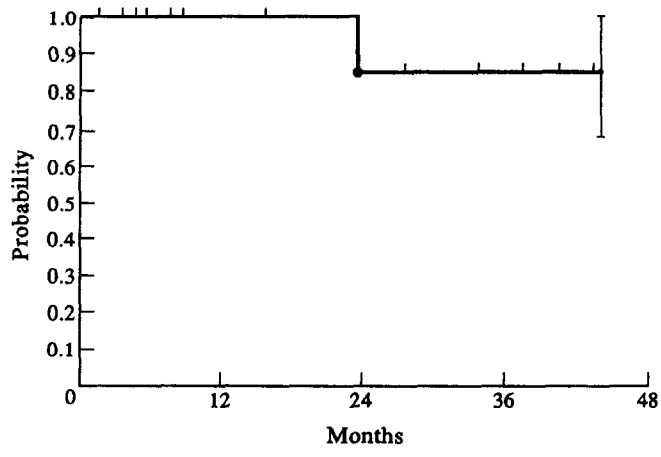

Figure 2. Relapse-free survival

administration and minimal local toxicity. Their antitumour activity was similar, but carboplatin was less toxic and better tolerated [7].

Pretreated ovarian cancer patients with minimal residual tumour were seen to achieve long-term remission after i.p. cisplatin-based chemotherapy [19, 20]. Whether this route can substantially increase the chance of cure in untreated ovarian cancer patients with little tumour burden, or whether it may prevent relapse in high-risk localised ovarian cancer, remains to be seen. Zambetti and colleagues [21] reported nine pCRs among 13 untreated patients with minimal residual disease after i.p. cisplatin plus cyclophosphamide. They observed two relapses at 20 and 36 months. On the basis of these results, they stated that perhaps the i.p. route did not contribute significantly to treatment of these patients, and suggested three possible causes: inadequate drug penetration into tumour nodules larger than 5 mm, uneven fluid distribution in the peritoneal cavity after repeated treatment cycles and unfavourable dose–response curve for cisplatin.

Our study was planned to evaluate, prospectively, whether short-term (to avoid adhesion formation), high dose intensity, weekly, i.p. treatment could improve response rate and survival in previously untreated patients with minimal tumour burden. We hypothesised that the addition of IFN to carboplatin would be an effective contribution to treatment due to its independent activity and ability to potentiate carboplatin cell kill. In this preliminary report, we present some important results of this study.

The combination caused severe toxicity in a very low percentage of patients. Local toxicity was minor, but the formation of wide peritoneal adhesions could indicate a restriction in the use of this combination. Assessment of fluid distribution during the treatment, by means of intraperitoneal contrast computed tomography, is warranted. Nevertheless, adhesion formation did not seem to impair the efficacy of treatment since 4/5 patients with adhesions showed no evidence of disease at second-look laparotomy, although response evaluation should be made with caution in these patients. It is likely that adhesion formation is not an early event, so a short-term high dose intensity treatment could eradicate the tumour before adhesions form.

Systemic side-effects were similar to those observed with i.v. carboplatin and IFN treatment [22, 23]. No treatment-related deaths occurred, although 5 patients required G-CSF administration because of grade 4 neutropenia. A dose intensity of carboplatin greater than 120 mg/m^2/week was achieved; this appears significantly higher than that achievable by standard carboplatin monthly schedule, especially considering the concomitant administration of high-dose interferon [24]. Moreover, a higher dose intensity could be possible by adding G-CSF at each course [25], although the capability of G-CSF to increase carboplatin doses is still controversial [26].

Since IFN-related side-effects were frequent and sometimes severe, its dosage should be reduced to improve tolerance.

The overall efficacy of the treatment was good: a 70% pCR rate was achieved in the 20 evaluable patients. Final conclusions cannot yet be drawn, in view of the low number of patients and the short follow-up. However, our results look interesting if we consider separately patients with tumours size smaller than 5 mm and those with larger tumours. The pCR rate was 91% (range 74–100) in the former and 44% (range 12–75) in the latter group. In view of this, we stopped enrolment of patients with smaller tumours since the 95% CI of the observed pCR rate exceeded the target percentage chosen (70%). Although the follow-up is too short to accurately determine the cure rate, it should be noted that the estimated overall survival at almost 4 years is 91% (range 83–99%), and 100% in those with $\leq$ 5 mm tumour size. The estimated relapse-free interval, 86% (range 73–99) at over 3 years (100% in patients with $<$ 5 mm tumour size), is also very encouraging. On the basis of these results, there seems to be an advantage for i.p. treatment in these patients. As expected, the cut-off lesion diameter was critical in this study. In fact, the pharmacokinetic advantage obtained by the i.p. route concerns only superficial cell layers [27], so only patients with very small tumours ($\leq$ 5 mm) may significantly benefit from this approach. Our results indicate the need for a randomised trial to discern advantages of this totally i.p. approach versus the best i.v. chemotherapy regimen (cyclophosphamide, doxorubicin, cisplatin, CAP) in these patients. This pharmacokinetic advantage could also benefit patients with poor prognosis localised tumour (I–II stage FIGO). It would also be interesting to evaluate the effects of the addition of truly non-cross-resistant drugs, such as mitoxantrone [28].

What is the best schedule of carboplatin administration: weekly or every 4 weeks? We think the weekly schedule allows a higher dose intensity and, above all, more frequent simultaneous exposition of tumour to the two drugs. In any case, a comparison between the two schedules is needed.

In conclusion, this i.p. immunochemotherapy combination seems a feasible approach to the treatment of previously untreated ovarian cancer patients with minimal tumour burden after primary surgery. It looks highly effective in patients with $\leq$ 5 mm tumour size. IFN dosage should be reduced to improve tolerance, and carboplatin doses (with G-CSF routine administration) could be increased as an attempt to improve efficacy. Further randomised trials are warranted to compare this approach to standard systemic treatment in patients with no or smaller than 5 mm residual tumour.

1. Ozols RF, Young RC. Chemotherapy of ovarian cancer. *Semin Oncol* 1991, **18**, 222–232.
2. Dedrick RL, Myers CE, Bungay PM, *et al.* Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rev* 1978, **62**, 1–9.
3. Howell SB, Pfeifle CE, Wung WE, *et al.* Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med* 1982, **97**, 845–851.
4. Reichman B, Markman M, Hakes T, *et al.* Intraperitoneal cisplatin and etoposide in the treatment of refractory/recurrent ovarian carcinoma. *J Clin Oncol* 1989, **7**, 1327–1332.
5. De Gregorio MW, Lum BL, Holleran WM, *et al.* Preliminary observations of intraperitoneal carboplatin pharmacokinetics during a phase I study of the Northern California Oncology Group. *Cancer Chemother Pharmacol* 1986, **18**, 235–238.
6. Elferink F, van der Vijgh WJF, Klein I, *et al.* Pharmacokinetics of carboplatin after intraperitoneal administration. *Cancer Chemother Pharmacol* 1988, **21**, 57–60.
7. Markman M, Hakes T, Reichman B, *et al.* Intraperitoneal cisplatin and carboplatin in the management of ovarian cancer. Sixth International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy. San Diego, 1991, 35.
8. Berek J, Hacker N, Lichtenstein A, *et al.* Intraperitoneal recombinant alpha-interferon for salvage immunotherapy in stage III epithelial ovarian cancer: a Gynaecologic Oncology Group study. *Cancer Res* 1985, **45**, 4447–4453.
9. Welander CE, Morgan TM, Homesley HD, *et al.* Combined recombinant human interferon alpha 2 and cytotoxic agents studied in the clonogenic assay. *Int J Cancer* 1985, **35**, 721–726.
10. Willemse PB, De Vries EGE, Mulder NH, *et al.* Intraperitoneal human recombinant inteferon alpha-2b in minimal residual ovarian cancer. *Eur J Cancer* 1990, **26**, 353–358.

11. Nardi M, Cognetti F, Pollera CF, *et al.* Intraperitoneal recombinant alpha 2 interferon alternating with cisplatin as salvage treatment for minimal residual disease ovarian cancer: a phase II study. *J Clin Oncol* 1990, **8**, 1036–1041.
12. Iaffaioli RV, Frasci G, Facchini G, *et al.* Alpha 2b interferon by intraperitoneal administration via temporary catheter in ovarian cancer. Preliminary data. *Eur J Gynecol Oncol* 1991, **12**, 69–75.
13. Berek JS, Welander C, Schink JC, Grossberg H, Montz FJ, Zigelboim J. Phase I–II trial of intraperitoneal cisplatin and α-interferon in patients with persistent epithelial ovarian cancer. *Gynecol Oncol* 1991, **40**, 237–243.
14. Repetto L, Chiara S, Guido T, *et al.* Intraperitoneal chemotherapy with carboplatin and interferon alpha in the treatment of relapsed ovarian cancer: a pilot study. *Anticancer Res* 1991, **11**, 1641–1643.
15. Mangioni C, Egres A, Landoni F, *et al.* A phase II study of cisplatin in a weekly schedule for advanced epithelial ovarian cancer. 14th International Cancer Congress, Budapest 1986, 3859 (abstract).
16. Young RC, Perez CA, Hoskins WJ. Cancer of the ovary. In De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer, Principles and Practice of Oncology*, 4th edition. Philadelphia, J.B. Lippincott Company, 1993, 1226–1263.
17. Dunnick WR, Jones RB, Doppman JL, *et al.* Intraperitoneal contrast infusion for assessment of intraperitoneal fluid dynamics. *AJR* 1979, **133**, 221–223.
18. Kaplan ES, Meier P. Non parametric estimation for incomplete observations. *J Am Stat Assoc* 1958, **53**, 557–580.
19. Howell SB, Zimm S, Markman M, *et al.* Long term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. *J Clin Oncol* 1987, **5**, 1607–1612.
20. Markman M, Reichman B, Hakes T, *et al.* Impact on survival of surgically defined favorable responses to salvage intraperitoneal chemotherapy in small-volume residual ovarian cancer. *J Clin Oncol* 1992, **10**, 1479–1484.
21. Zambetti M, Gianni L, Escobedo A, Pizzetti P, Spatti GB, Bonadonna G. First-line chemotherapy with intraperitoneal cisplatin and intravenous cyclophosphamide in ovarian carcinoma. A preliminary report. *Am J Clin Oncol* 1989, **12**, 118–122.
22. Canetta R, Bragman K, Smaldone L, *et al.* Carboplatin: current status and future prospects. *Cancer Treat Rev* 1988, **15**(suppl.B), 17–32.
23. Quesada JR, Talpaz M, Rios A, *et al.* Clinical toxicity of interferons in cancer patients: a review. *J Clin Oncol* 1986, **4**, 234–243.
24. McVie JG, ten Bokkel Huinink W, Dubbelman R, *et al.* Phase I study and pharmacokinetics of intraperitoneal carboplatin. *Cancer Treat Rev* 1985, **12**(suppl.A), 35–41.
25. De Vries EGE, Biesma B, Willemse PHB, *et al.* A double-blind placebo-controlled study with granulocyte–macrophage colony-stimulating factor during chemotherapy for ovarian carcinoma. *Cancer Res* 1991, **51**, 116–122.
26. Rusthoven J, Levin L, Eisenhauer E, *et al.* Two phase I studies of carboplatin dose escalation in chemotherapy-naive ovarian cancer patients supported with granulocyte-colony stimulating factor. *JNCI* 1991, **83**, 1748–1753.
27. Los G, Mutsaers PHA, van der Vijgh WJF, *et al.* Direct diffusion of *cis*-diamminedichloroplatinum (II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res* 1989, **49**, 3380–3384.
28. Markman M, George M, Hakes T, *et al.* Phase II trial of intraperitoneal mitoxantrone in the management of refractory ovarian carcinoma. *J Clin Oncol* 1990, **8**, 146–150.

Pergamon

European Journal of Cancer Vol. 30A, No. 7, pp. 950–954, 1994

0959–8049/94 $7.00 + 0.00

0959-8049(94)E0042-3

A Phase I–II Study of *N*-(Phosphonacetyl)-L-Aspartic Acid (PALA) Added to 5-Fluorouracil and Folinic Acid in Advanced Colorectal Cancer

D.I. Jodrell, W. Oster, D.J. Kerr, P.A. Canney, H. Yosef, W.P. Steward, S.B. Kaye and J. Cassidy

***N*-(phosphonacetyl)-L-aspartic acid (PALA) inhibits the enzyme L-aspartic acid transcarbamoylase (ATCase) which is important in *de novo* pyrimidine synthesis. Low dosages of PALA modulate the *in vitro* activity of 5-fluorouracil (5-FU) and PALA (250 mg/m²) inhibits pyrimidine synthesis in patients. PALA (250 mg/m² day 1) was combined with an established 5-FU/folinic acid (FA) regimen [FA (200 mg/m² over 2 h days 2+3) and bolus and 22 h infusional 5-FU (300–500 mg/m² days 2+3)] without the need for dose reduction of 5-FU or FA. 35 patients were entered. Treatment was well tolerated; 4/27 patients experienced ≥ ECOG grade 3 toxicity at full 5-FU dosage (500 mg/m² bolus/infusion). However, the response rate in 33 evaluable patients was only 6.1% [95% confidence intervals (C.I.) 0.2–21.8%]. Median response duration was short (4 months, 95% C.I. 3–6 months) and overall median survival was 10 months (95% C.I. 7–16 months). Although PALA (250 mg/m²) can be combined with full dosage 5-FU/FA, the combination has poor activity in colorectal cancer.**

Key words: PALA, 5-fluorouracil, folinic acid, colorectal cancer
Eur J Cancer, Vol. 30A, No. 7, pp. 950–954, 1994

INTRODUCTION

TO DATE, response rates achieved in patients with metastatic colorectal cancer have been disappointing. The fluorinated pyrimidine, 5-fluorouracil (5-FU) is the most extensively used drug in metastatic colorectal cancer, although a meta-analysis [1] has shown that the response rate achieved using conventional bolus administration schedules is only 11%. Because of this low response rate, interest has focused on the modulation of 5-FU activity.

N-(phosphonacetyl)-L-aspartic acid (PALA) is an inhibitor of the enzyme L-aspartic acid transcarbamoylase (ATCase) which is important in *de novo* pyrimidine synthesis. At high concen-