Eur J Cancer, Vol. 27, No. 6, p. 804, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00

Letters

Sequential Proleukin (rIL-2) by Continuous Infusion with Cisplatin and Cyclophosphamide in Patients with Unresectable Ovarian Cancer

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OVARIAN CANCER is the most common cause of death among women with gynaecological maligancies. Most patients present with FIGO stage III or IV. The overall 5-year survival rate is 10%. Recent clinical evidence suggests that interleukin-2 (IL-2) may be effective in the treatment of ovarian cancer for patients with residual bulky tumour after primary debulking [1–3, 5].

In May 1989 we started an open non-randomised phase II study to evaluate the toxicity and efficacy of a combination of cisplatin and cyclophosphamide followed by continuous infusion of IL-2 in patients with unresectable ovarian cancer. Patients eligible for this trial received on day 1 cisplatin (100 mg/m^2) and cyclophosphamide (600 mg/m^2). Following 2 weeks rest, a continuous intravenous rIL-2 infusion was started for 5 days (120 h) at 3×10^6 Cetus units/m^2 per day. After 2 weeks rest, in the absence of undue toxicity or tumour progression, patients received further cycles of treatment with a maximum of 6 cycles.

The infusion of rIL-2 was interrupted if severe toxicity—severe hypotension, cardiac arrhythmias, myocardial ischaemia, agitation or confusion, serum bilirubin of >5 mg/dl or serum creatinine of >4.5 mg/dl, bacterial sepsis or dyspnoea at rest—occurred.

Between May 1989 and August 1990, 10 patients with histologically confirmed ovarian cancer were enrolled in this phase II trial. Intensive care was planned during the rIL-2 infusion. WHO toxicity evaluation criteria were adopted.

In total, the 10 patients received 160 days of rIL-2 infusion. Globally, 42 courses of treatment were administered. Ten of the 42 courses were discontinued due to subjective intolerance or toxicity. Of the completed courses, in 28 we administered the full dose of rIL-2 and in 4 courses the dose was reduced.

No toxic deaths were observed. Grade IV toxicity was seen in 2 patients (renal failure and severe thrombocytopenia). Grade III toxicities were frequent—hypotension (32%), weight gain (23%), fever chills (18%), desquamation ulceration (36%), vomiting or nausea (27%), renal disorders (18%), dyspnoea (27%), haematological problems (18%), arrhythmia (14%), capillary leak syndrome (23%), CNS disorders (14%)—but they disappeared in all cases when the rIL-2 infusion was interrupted. During the rIL-2 infusion all patients experienced a rash and in 36% we found severe desquamation. Fever and gastrointestinal toxicity with nausea/vomiting and diarrhoea also occurred in all patients with severe toxicity in 18% and 27%, respectively, needing intravenous fluids.

Clinical management of patients during the combination of chemotherapy with continuous infusion of rIL-2 remains very difficult and intensive care is essential. The most frequently reported toxicities include renal and hepatic dysfunction and capillary leak syndrome.

As noted by Paciucci *et al.* [4] severe thrombocytopenia can be a clinically important toxic side-effect, particularly if platinum containing cytostatic agents with thrombocytopenic and nephrotoxic effect are used in combination with continuous rIL-2.

All patients experienced severe side-effects which significantly influenced compliance.

In conclusion, the investigative study of advanced ovarian cancer stage III or IV with cyclophosphamide and cisplatin in combination with continuous infusion of rIL-2 should be restricted to oncological centres because of the high rate of systemic side-effects.

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Revised 26 Feb. 1991; accepted 6 Mar. 1991.

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Eur J Cancer, Vol. 27, No. 6, pp. 804–805, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00

Phase II Study of Navelbine in Advanced Renal Cell Carcinoma

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VINBLASTINE achieved a mean response rate of 17% (range 0–31%) in 626 patients entered in 15 phase II trials. Combination therapy does not seem to obtain better results than vinblastine alone [1, 2]; nor do the new biological response modifiers significantly improve this therapeutic effect [3, 4].

Navelbine (5'-nor-anhydrovinblastine, vinorelbine) is a new semisynthetic compound derived from the vinca alkaloid series.

In P388 and L 1210 leukaemia, navelbine has been shown to possess a higher cytotoxic activity than vincristine and vinblastine. Moreover, in B16 melanoma, where the other vinca alkaloids are inactive, a significant cytotoxic effect suggesting a broader antitumour activity has been reported [5, 6]. In phase II studies, navelbine has shown a higher antitumour activity than vincristine and vinblastine in breast, lung and ovarian carcinoma [7–9].

These findings prompted us to evaluate navelbine as first-line single agent chemotherapy in patients with advanced renal cell carcinoma.

15 consecutive patients with histologically confirmed renal cell carcinoma entered this phase II study. All patients had advanced objectively measurable disease, a performance status of 2 or lower (WHO scale), age 75 years or under and a life expectancy of at least 12 weeks. Patients previously treated with chemotherapy and/or immunotherapy or with disease localised only at a previously irradiated site were excluded from the study. At least 4 weeks had to elapse between previous treatment and administration of navelbine. Other eligibility criteria were peripheral white blood cell (WBC) count of at least 2000/μl and a platelet count of at least 100 000/μl, bilirubine and creatinine 1.25 × N (upper limit of normal values) or less and no pathological signs of peripheral neuropathy, unless dependent on the malignant disease.

Pretreatment evaluation included clinical history, physical examination with documentation of all signs and symptoms of disease with particular attention to measurable lesions, complete blood count, blood chemistry, electrocardiogram, chest X-ray, bone scan and additional radiographical or ultrasound studies when clinically indicated. Physical examination, complete blood count and blood chemistry were repeated every week. Bone scan, X-ray and ultrasound studies, when necessary for disease evaluation, were repeated every eight cycles.

Navelbine was given at a dose of 30 mg/m^2 diluted in 250 ml of normal saline in an intravenous infusion of at least 20 minutes, weekly. Prophylactic antiemetic treatment with 20–40 mg metoclopramide was routinely given. Treatment was continued until disease progression, severe toxicity or patient's refusal. Drug administration was delayed by 1 week in the case of no full haematological recovery (WBC less than 2000/μl and/or platelets less than 100 000/μl) at the scheduled retreatment time. If haematological toxicity imposed a treatment interruption of at least 3 weeks, the dose was decreased to 25 mg/m^2, but the same frequency of administration was maintained. Criteria used for judging response and toxicity were those recommended by the WHO. Only patients receiving at least eight cycles were suitable for assessment of response.

The main pretreatment patient characteristics are summarised in Table 1. 15 patients were registered in the study. 1 patient was ineligible because of previous treatment with vinca alkaloids and 14 patients were fully evaluable for clinical response and toxicity. No patient responded to treatment. 5 patients showed stable disease with a median duration of 12 weeks and 9 patients showed disease progression. The overall median survival was 8 months (range 3–36).

Table 1. Patients' characteristics

Evaluable patients	14
M/F	8/6
Median age (range)	65 (37–77)
Median initial performance score (range)	0 (0–2)
Prior surgery	14
Median DFI (mo) (range)	6.5 (0–24)
Dominant metastatic sites of disease	
Soft tissue	1
Visceral	12
Bone	1
Metastatic sites of disease	
Nodes	4
Adrenal	2
Retroperitoneum (renal lodge)	5
Lung	7
Bone	4
Liver	5

DFI = disease-free interval.

Toxicity was evaluated on 157 cycles and was generally mild, without any life-threatening complication. The median number of courses was 9 (range 8–28). Leukopenia was infrequent but always manageable and reversible. Leukopenia grade 3–4 occurred in 28.5% of patients. Anaemia grade 2-3 was observed in 14.2% of patients. Thrombocytopenia was never reported. Nausea and vomiting grade 1-2 have been observed in 21.5% and alopecia in 14.2% of patients. Neurotoxicity developed in about 30% of patients, but was generally mild and consisted mainly of paresthesia constipation and myalgia.

We conclude that with the dose and schedule employed, the antitumour activity of navelbine was negligible.

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Revised 4 Mar. 1991; accepted 6 Mar. 1991.

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