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# 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 $3 \times 10^6$ 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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## Phase II Study of Navelbine in Advanced Renal Cell Carcinoma

Luciano Canobbio, Francesco Boccardo, Domenico Guarneri, Caterina Calabria, Andrea Decensi, Antonio Curotto, Giuseppe Martorana and Luciano Giuliani

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.