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Short Communication

Effects of Interleukin-1α on Ovarian Carcinoma in Patients with Recurrent Disease

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The aim of this study was to evaluate the safety and the biological effects of interleukin (IL-1α) in patients with recurrent ovarian carcinoma treated with carboplatin. In this phase I study, IL-1α was administered by a continuous intravenous infusion at doses ranging 0.1–10 μg/m² every 24 h for 4 days (96 h) 3 weeks before the first dose of carboplatin (400 mg/m²) in patients with potentially platinum-sensitive ovarian cancer. The maximum tolerated dose was 3 μg/m²/day. Dose-limiting effects at 10 μg/m²/day were fever, chills, hypotension and fluid retention. Minor but objective antitumour effects were observed in 2 of 18 patients. 4 patients (including 1 with a minor response) had a decrease of the CA-125 serum level ranging from 33 to 39%. The trial design precluded evaluation of the duration of response to single-agent IL-1α. Based on this trial design, there is evidence of minor antitumour effect to a single course of IL-1α dose given prior to chemotherapy.

Key words: ovarian carcinoma, platinum-sensitive, interleukin-1-alpha, response rate, myelosuppression

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INTRODUCTION

INTERLEUKIN (IL)-1 IS a mediator of the host response to infection, inflammation, immunological reaction and tissue injury. It has multiple biological effects including induction of fever through the hypothalamus, hepatic synthesis of acute phase proteins, proliferation of thymocytes, activation of T and B lymphocytes, proliferation of fibroblasts and the production of adrenocorticotropic hormone by the pituitary gland with a subsequent increase of corticosterone blood level [1]. In addition, IL-1 has been shown to augment natural killer cell activity, antibody-dependent cellular toxicity and macrophage tumoricidal activity. IL-1 exists in two forms [2] (IL-1α and IL-1β) that bind to the same receptors and appear to have identical biological activities [3].

Recombinant human (RHu)-IL-1α has been efficiently expressed by *Escherichia coli* and purified to homogeneity [4]. The recombinant protein, rHu-IL-1α, exhibits biological functions similar to those of the natural molecule: (i) the ability to stimulate thymocyte mitogenesis through stimulation of IL-2 production and (ii) direct cytotoxic and/or growth-inhibitory effects on various tumour cell lines (A375 melanoma, human mammary carcinomas MCF-7, T47D, and MDA-MB-415 [5], myeloid leukaemia [6], rhabdomyosarcoma A 673 and adenocarcinoma of the lung [7]).

rHu-IL-1α has been investigated mainly for its ability to potentiate the haematopoietic response. Preclinical studies have demonstrated the *in vivo* haematopoietic effects of IL-1 in normal and myelosuppressed animals. In several human clinical trials, a protection against myelosuppression has been observed after exposure to rHu-IL-1α [8–10].

On the basis of the documented clinical ability of IL-1 to act as a multilineage inducer of haematopoiesis and the preclinical observations of direct antitumour activity, we designed a phase I trial to evaluate the protective effects of IL-1α from carboplatin-induced myelosuppression in patients with recurrent ovarian carcinoma. The results of this trial were published elsewhere [11]. In this report, we describe clinical evidence of the antitumour effect of rHu-IL-1α observed in some patients.

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PATIENTS AND METHODS

Patients with a histologically confirmed diagnosis of recurrent ovarian carcinoma considered to be potentially platinum-responsive (response to a prior platinum-based therapy with a 6-month minimum interval since their most recent platinum treatment) were eligible. All patients had a good performance status (Zubrod <2), adequate renal function (serum creatinine <2.0 mg/dl and creatinine clearance >60 ml/min), normal hepatic function (total bilirubin level <1.5 mg/dl), prothrombin time <1.3 times the control value and a life expectancy of at least 3 months. Written informed consent was obtained from all patients before entry into the study in accordance with institutional guidelines.

Before and during the course of the clinical trial, the patients were evaluated with a complete history, a physical examination and specific laboratory tests (complete blood cell counts with differential, serum chemistry and coagulation profiles, urinalysis, chest X-ray and electrocardiogram). Blood counts were performed at least three times a week. Tumour response was evaluated by a periodic physical examination, appropriate imaging studies and the tumour marker CA-125 serum level.

rHu-IL-1α was prepared by Immunex Corporation (Seattle, Washington, U.S.A.) from a cDNA clone expressed in *E. coli*. The molecular weight of rHu-IL-1α is approximately 17.5 kDa. The purified protein has a specific activity of 5×10^9 U/mg of protein. A unit is defined as the amount of cytokine necessary to induce a 50% inhibition of the maximum proliferation in the murine thymoma cell line (EL-4) assay.

The study was divided into three cycles followed by maintenance therapy in patients with evidence of a haematopoietic response or an antitumour response to rHu-IL-1α alone. In the first cycle, rHu-IL-1α was given as a single agent by continuous intravenous infusion daily for 96 h. This cycle was administered to evaluate clinical tolerance and biological effects of rHu-IL-1α alone. In subsequent cycles, carboplatin was studied with or without rHu-IL-1α. This report analyses only the response to the first cycle with rHu-IL-1α alone. The primary end point after rHu-IL-1α administration was to determine the maximum tolerated dose (MTD). Therefore, doses of rHu-IL-1α ranging from 0.1 to 10 μg/m²/day for 4 days were tested. 3 patients were entered at each dose level: 0.1, 0.3, 1.0, 3.0 and 10 μg/m²/day. An additional 3 patients were entered at 3 μg/m²/day after this dose was determined to be the MTD. The secondary end point was to detect any evidence of haematopoietic or antitumour responses.

A partial response is defined as a reduction of at least 50% of the size of the tumour measured as the product of the cross-sectional diameters. A minor response is defined as a 50–25% reduction in the size of the tumour. Stable disease is a <25% variation in the size of the tumour. Given the nature of this trial (all patients received carboplatin 3 weeks after the first dose of IL-1α), the duration of the antitumour response to IL-1α alone could not be evaluated in this trial.

RESULTS

18 patients with a median age of 54 years (range 29–68 years) were evaluated (Table 1) for the effects of rHu-IL-1α given as a single agent. Their median performance status was 1 on the Zubrod scale (range 0–2). The number of prior chemotherapy regimens was 2 (range 1–4).

Both serological and clinical responses were elicited with this agent (Table 2). Two minor responses were observed (patients 3 and 13) and one mixed response was seen with a partial remission in the lymph node site but very little regression in the pelvic mass (patient 14). Responding tumour sites included mainly soft-tissue and lymph node metastases. A 30% or more decrease of the CA-125 serum level was observed in 4 patients: decrease of 33% (patient 5), 34% (patients 7 and 15), and 39% (patient 3). Of these, patients 1 had both a minor response and a 39% decrease of the CA-125 serum level (patient 3). Responses were noted throughout the entire range of dose levels. The distribution of the responders at different dose levels of IL-1α is shown in Table 2. A suggestion of antitumour activity was seen in all patients (13, 14 and 15) entered at the highest dose level (one level above MTD).

Table 1. Patient characteristics

Number of patients	18
Age (years)	
Median	54
Range	29–68
Prior treatments	
Platinum-based i.v.	24
Other chemotherapy	4
Hormonal therapy	6
Platinum i.p.	3
^{90}Yttrium-B72.3 MAb i.p.	4
^{32}P i.p.	1
Interferon i.p.	2

i.v., intravenous; i.p., intraperitoneal; MAb, monoclonal antibody.

Main side-effects included fever and chills (100%), nausea and vomiting (86%), tachycardia (81%), myalgia (71%), headache (67%), fatigue (67%), anorexia (67%) and diarrhoea (43%) and were observed at ≥3 μg/m²/day. Fever, chills, hypotension and fluid retention were the dose-limiting toxic effects at 10 μg/m²/day. None of the patients required vasopressor support. Fever and chills were managed with around-the-clock acetaminophen, diphenhydramine and/or meperidine. Intravenous fluids were routinely administered for hydration and to maintain blood pressure.

A more detailed discussion of the haematopoietic results is published elsewhere [11]. Treatment with rHu-IL-1α before chemotherapy resulted in a dose-dependent increase in leucocytes, usually within 24 h. In contrast, a transient decrease in platelets was seen during the infusion of IL-1α, with a significant increase in the platelet counts after the discontinuation of rHu-IL-1α. In addition, there was a transient decrease in the haemoglobin levels (from a mean of 12 to 10 g/dl), which returned to baseline after the discontinuation of the infusion.

DISCUSSION

To our knowledge, this is the first report of activity with rHu-IL-1α in patients with epithelial ovarian cancer. rHu-IL-1α used as a single agent elicited some antitumour effects in a few patients previously treated with chemotherapy. Antitumour activity was observed at each dose of rHu-IL-1α, and all patients treated at the highest dose (10 μg/m²/day) exhibited some antitumour effect. The efficacy of a higher dose of IL-1α needs further evaluation.

In the 3 patients who experienced a minor or mixed response, activity was noted exclusively in lymph nodes or soft-tissue metastases (breast, skin and bone). The responding

Table 2. Response to rHu-IL-1α as a single agent

Patient	rHu-IL-1α dose (μg/m²/d > 4 days)	CA-125 serum level [U/ml (% change)] Pretreatment	On day 4	On day 21	Tumour response On day 4	On day 21
3	0.1	173	—	106 (–39%)	Lymph node: PR	Lymph node: MR
5	0.3	150	—	101 (–33%)	NE	NE
7	1.0	145	—	95 (–34%)	Vaginal mass: MR	Vaginal mass: SD
11	3.0	1274	—	1184 (–7%)	ND	Vaginal mass: SD
18	3.0	976	784 (–19%)	794 (–19%)	ND	Pelvic mass: SD
13	10	714	—	669 (–6%)	ND	Soft tissue masses: MR
14	10	3633	3652 (+0.5%)	4574 (+26%)	Lymph nodes: PR; Pelvic masses: ND	Lymph nodes: PR; Pelvic masses: SD
15	10	10247	6750 (–34%)	9236 (–10%)	Lymph node: PR	Lymph node: SD

MR, minimal response; SD, stable disease; NE, could not be evaluated; ND, not done; PR, partial response.

tissues were not evaluated histologically, therefore it is not possible to exclude a decrease of the lymphocytic population infiltrating the metastasis versus a true tumoricidal effect to account for the observed effect. However, in 4 patients, including 1 with a minor response, a >30% decrease of CA-125 serum level was noted. In 3 of these patients, a reduction in the indicator mass (two lymph node sites and one vaginal mass) was observed immediately after the completion of rHu-IL-1α treatment (on day 4). This effect was not sustained for more than 2 weeks. Because of the design of this study, patients treated with single-agent IL-1α could be observed for only 3 weeks regardless of the response status. Better antitumour activity might be demonstrated with different schedules of rHu-IL-1α.

In vitro experiments have shown that 2 to 3 units of IL-1 induce a 50% inhibition of the proliferation of the human ovarian carcinoma OVCAR-3. The maximum inhibition is achieved at concentrations of 10 U/ml for 3 days. This inhibition can be prevented by rHu-IL-1 receptor antagonist [12]. Synergistic antiproliferative effects are achieved with IL-1 and alpha interferon [13]. In the murine tumour models RIF-1 fibrosarcoma and Panc 02 pancreatic adenocarcinoma, acute intratumoral haemorrhagic responses were observed after rHu-IL-1 injections [14]. These results suggest that rHu-IL-1α may have an antitumour potential either alone or in combination. Objective responses with this agent have been reported for patients with other neoplasms. Starnes and associates reported responses with 5 days of IL-1β infusion in 3 of 9 patients with malignant melanoma [8]. However, Smith and associates were not able to reproduce these results in patients with melanoma [9] or other advanced tumours such as gastrointestinal cancers [10].

This is the first report of clinical antitumour activity of a single 3-week course of IL-1α in patients with advanced recurrent ovarian cancer. It is difficult to determine the efficacy of a drug administered for only one course (prior to chemotherapy). However, the clinical observation (i.e. decreased CA-125 with some tumour regression) is worth further investigation of the drug's activity in a formal clinical trial.

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