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Short Communication

Serum Interleukin 1 in Ovarian Cancer Patients

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Interleukin-1 (IL-1) is a multifunctional cytokine playing a central role in the immune response and displaying direct cytotoxic activity *in vitro*. Serum IL-1α and β levels were measured by enzyme linked immunosorbent assay (ELISA) in 75 ovarian cancer patients, 30 patients with benign ovarian cysts and 50 healthy controls. Both serum IL-1α and IL-1β levels were more often elevated in ovarian cancer patients compared with healthy controls (chi-square test, $P < 0.001$ and $P < 0.001$, respectively). Mean serum IL-1α and β levels decreased significantly after surgical intervention (paired *t*-test, $P = 0.0001$ and $P = 0.0002$, respectively). No correlation with histopathological parameters and overall and disease-free survival was found. These preliminary results indicate that serum levels of IL-1α and β represent a host defence reaction rather than an autonomous tumour cell production. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

OVARIAN CANCER is a relatively rare disease, yet it is one of the leading causes of cancer death in females [1, 2]. It is now known that the human female host is able to recognise ovarian tumour cells as foreign and to initiate an immune response involving specific antibody molecules [3].

Interleukin-1 (IL-1) is a cytokine with multiple biological activities. IL-1α and IL-1β are two structurally related polypeptides that show approximately 25% homology at the amino acid level. The genes for the production of both IL-1 molecules are located on chromosome 2. IL-1 is produced by a wide variety of cells in response to stimuli, i.e. inflammatory agents, infections or microbial endotoxins [4]. The multiple functions of IL-1 establish it as a lymphokine with a central role in the immune response.

Target cells of the immunological effects of IL-1 are macrophages, monocytes, B-lymphocytes, T-lymphocytes, natural killer (NK) cells and lymphokine-activated killer (LAK) cells. IL-1 has been shown to induce the cytotoxic activity of these cells in tumour cell lines and to display direct cytotoxic activity in certain tumour cell lines *in vitro* [5–7]. IL-1 also has indirect antitumour effects by synergising with other lymphokines, e.g. interleukin-2 and -6 [4]. *In vivo*, the possible antitumour effect of IL-1 may be the result of the sequential activation of cells of the immune system by activation of the lymphokine cascade [4].

The present study was performed to determine more about the clinical value of serum IL-1 levels in patients with ovarian cancer.

PATIENTS AND METHODS

This retrospective study included serological examinations of 75 patients suffering from ovarian cancer FIGO stages Ia ($n = 28$), Ic ($n = 21$), II ($n = 15$) and III ($n = 11$). The median age at the time of diagnosis was 49.8 years (range 34–71). Histologically, 38 tumours were graded as serous adenocarcinomas, 26 as mucinous adenocarcinomas and 11 as other kinds of ovarian cancer. All patients underwent hysterectomy, oophorectomy, pelvic lymph node dissection and omentectomy. In stages Ic to III, a platinum-containing chemotherapy regimen was given. All patients underwent a close follow-up in 3 month intervals, including vagino-rectal palpation, abdominal ultrasound examination and tumour marker evaluation. Serum samples were collected at every visit. In cases of clinically doubtful findings and/or tumour marker elevation, computed tomography was performed. The range of follow-up was 8–95 months. 24 patients developed

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recurrent disease after primary therapy with a median disease-free interval of 21 months (range 7–32). 19 patients died of the disease.

Serum levels of IL-1 were evaluated in samples taken prior to surgery and 2 weeks after surgery. In patients with recurrent disease, serum levels of IL-1 were also evaluated in samples taken 3 months before diagnosis of recurrent disease. Serum samples ($n = 30$) were obtained from other patients undergoing laprascopic surgery because of a benign cystic tumour. Serum levels of IL-1 were additionally evaluated in a panel of 50 healthy blood donors.

Assay

Blood was collected by vein puncture and the serum samples obtained after clotting and centrifugation were stored in aliquots at −80°C. Serum levels of IL-1 were measured using the human IL-1 immunoassay (Quantikine, R&D Systems, Inc., Cambridge, Massachusetts, U.S.A.). All tests were carried out in duplicate according to the manufacturer's instructions. According to the manufacturer, the minimal detectable level is 0.3 pg/ml for IL-1α and 0.2 pg/ml for IL-1β. Intra-assay and interassay reproducibility was between 1.2 and 8.6%.

Statistical analysis

Comparisons between unpaired groups were made using the Mann–Whitney *U*-test. Comparisons between paired groups were made using a paired *t*-test. Survival probabilities were calculated by the product limit method of Kaplan and Meier. Univariate analysis was assessed using the log-rank test. Results were analysed for the end points of disease-free and overall survival. $P < 0.05$ was considered statistically significant. The SAS statistical software system (SAS Institute Inc., Cary, North Carolina, U.S.A.) was used for the calculations.

RESULTS

Serum levels of IL-1α were elevated prior to therapy in 18 ovarian cancer patients, but in none of the 30 patients with benign cysts nor the 50 healthy controls. This difference was statistically significant (chi-square test, $P = 0.003$ and $P < 0.001$ [monotone likelihood], respectively). The mean serum levels of IL-1α prior to primary surgery and 2 weeks after surgery were 0.99 pg/ml (standard deviation (S.D.) 1.13) and 0.47 pg/ml (S.D. 0.84) (paired *t*-test, $P = 0.0001$, Figure 1).

In the 50 healthy controls, the 95th percentile of serum IL-1β levels was 0.52 pg/ml. Among the 30 patients with benign cysts, 4 patients had elevated serum IL-1β levels, whereas in the 75 ovarian cancer patients IL-1β was elevated prior to therapy in 23 patients (chi-square test, $P < 0.001$ [monotone likelihood] and $P = 0.06$, respectively). In contrast to IL-1α, serum levels of IL-1β were significantly more often elevated in patients with benign tumours compared with healthy controls (chi-square test, $P = 0.008$).

Mean serum levels of IL-1β prior to primary surgery and 2 weeks after surgery were 12.47 pg/ml (S.D. 25.76) and 6.45 pg/ml (S.D. 18.5) (paired *t*-test, $P = 0.0002$, Figure 2).

Pretherapeutic serum levels of IL-1α and IL-1β showed no correlation with FIGO stage (Mann–Whitney *U*-test, IL-1α $P = 0.18$ and IL-1β $P = 0.44$), lymph node involvement (Mann–Whitney *U*-test, IL-1α $P = 0.71$ and IL-1β $P = 0.44$) and histological grading of tumour cells (Mann–Whitney *U*-test, IL-1α $P = 0.35$ and IL-1β $P = 0.30$).

We found no difference in serum IL-1α and IL-1β levels in patients with positive and negative inflammatory stromal component in the tumour tissue (Mann–Whitney *U*-test, $P = 0.3$).

24 patients relapsed after complete remission. In these patients, no increase of serum IL-1 levels before the detection of relapse was observed. In patients who relapsed, the median time interval between last blood sampling and relapse was 2.1 months (minimum 0.5, maximum 3). We did not observe a continuous rise in IL-1α and IL-1β in patients after clinical relapse.

The mean serum levels of IL-1α prior to therapy in patients with and without recurrence were 0.32 pg/ml (S.D. 1.08) and 0.28 pg/ml (S.D. 0.73), respectively (Mann–Whitney *U*-test, $P = 0.86$). The mean serum levels of IL-1β prior to therapy in patients with and without recurrence were 9.88 pg/ml (S.D. 28.26) and 2.77 pg/ml (S.D. 4.51) (Mann–Whitney *U*-test, $P = 0.71$), respectively.

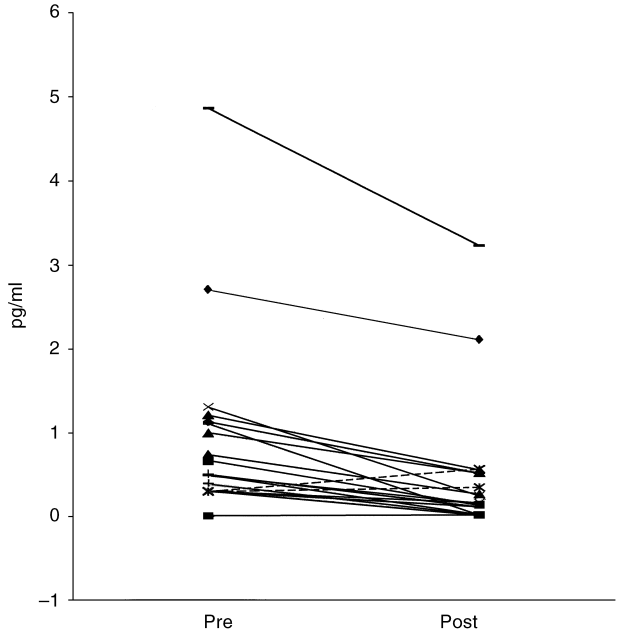

Figure 1. Serum interleukin-1α levels in patients with ovarian cancer prior to (Pre) and after therapy (Post).

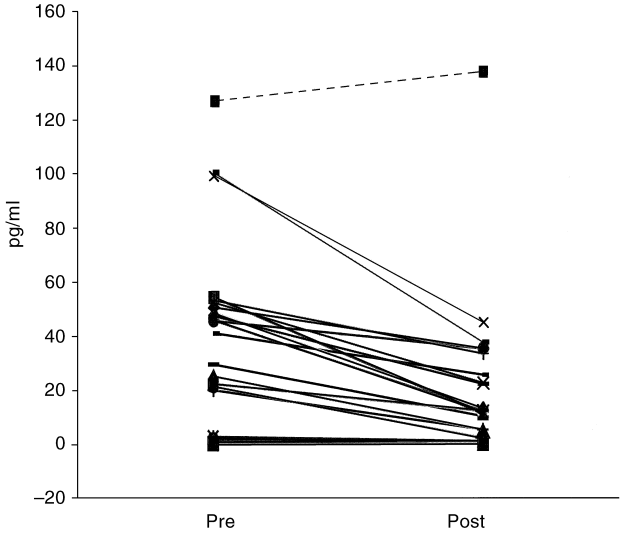

Figure 2. Serum interleukin-1β levels in patients with ovarian cancer prior to (Pre) and after therapy (Post).

According to the 95th percentile of serum concentrations measured in 50 healthy controls, cut-off values of 0.52 pg/ml for IL-1β and 0 pg/ml for IL-1α were selected. Elevated serum IL-1 levels prior to therapy were associated with a poorer disease-free interval, but this was not statistically significant (log-rank test, IL-1α $P = 0.09$ and IL-1β $P = 0.08$). No correlation with overall survival was found (log-rank test, IL-1α $P = 0.24$ and IL-1β $P = 0.20$).

DISCUSSION

In the present study, we evaluated the serum IL-1α and β levels in patients treated for ovarian cancer. We found a statistically significant difference in the serum IL-1α and β levels between patients with ovarian cancer and healthy controls. These findings are in accordance with previously reported data describing pretherapeutically elevated serum IL-1 levels in patients with liver and gastrointestinal cancers [8, 9]. The pre-operative serum levels of IL-1α and β have been measured in ovarian cancer by Moradi and colleagues [10], but these cytokines did not show any significant difference in the mean values when compared with healthy controls. IL-1β was measured by Punnonen and associates [11] in 15 serum samples of patients suffering from ovarian cancer, but was detected in none. These results might be due to the small numbers investigated. In a previous study, Nakazaki [8] demonstrated that cytokine peaks after operation were similar in patients with gallbladder stones and in gastrointestinal cancer patients. It was assumed that the cytokines are induced by each other, forming a complicated cytokine network after the onset of surgical infection. In our series, we found a significant decrease of serum IL-1 levels after debulking and completion of the wound healing process. Punnonen and associates [11] reported that the clinical stage of the ovarian cancer patients did not correlate with the level of cytokine production. The data collected in the current investigation confirm these findings. In our patients, we found no correlation of serum IL-1 levels with established prognostic parameters, such as stage, grading of tumour cells and pelvic lymph node involvement. Patients with recurrent disease and elevated serum IL-1α and β levels prior to therapy demonstrated a trend to a poorer disease-free survival. However, this difference was not statistically significant.

It has been reported that elevated serum IL-1 levels in cancer patients are due to autocrine production of tumour cells [12]. Haskill and colleagues [13] demonstrated the infiltration of significant numbers of T-lymphocytes and macrophages into ovarian tumour tissue. There is also evidence that tumour infiltrating cells contribute to elevated serum IL-1 levels [14]. Production of IL-1 in tissues may contribute to local paracrine effects, such as fibrosis, tissue matrix breakdown or the influx of inflammatory cells. Our results confirm that the production of IL-1 in ovarian cancer patients may be interpreted as a non-specific reaction of the inflammatory process rather than as a specific response to malignant cells [3, 11]. In this context it is important to also evaluate serum IL-1α and β levels in benign conditions. For this purpose, serum samples were obtained from patients undergoing laprascopic surgery because of a benign ovarian tumour. IL-1α was virtually absent, while detectable amounts of IL-1β were found in sera of women with benign ovarian tumours. Punnonen and associates [11] detected IL-1β at relatively high levels in the tumour tissue, but no significant difference was found in the production of these cytokines when benign and malignant tumours were compared. These results are confirmed by our data. It is of interest that we could find a statistically significant difference between the serum IL-1β levels of healthy controls and patients with benign tumours. Together, these findings indicate that non-specific immunological activation by benign and malignant ovarian neoplasms leads to the production of multifunctional cytokines, such as IL-1.

In summary, our data show that serum IL-1 levels are significantly higher in tumour patients compared with healthy controls. Serum IL-1 levels were not correlated with prognosis and histopathological parameters. Further studies are justified in order to clarify the role of IL-1 in the physiological host defence mechanisms against malignancies.

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