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Serum interleukin-2 levels in malignant melanoma patients

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In a majority of human neoplasms a mitogen mediated decrease in the production of interleukin 2 (IL-2) in vitro can be observed. Poor resolution of the available tests does not enable the evaluation of spontaneous and in vivo IL-2 production in cancer patients. Using ELISA method (Genzyme), serum IL-2 concentrations were determined in malignant melanoma patients and healthy controls. The mean value (±SE) of serum IL-2 in 30 healthy donors was 269 U/ml (269 ± 66). In patients with malignant melanoma this value was lower - 37 U/ml (37 ± 16). The difference between mean values of both groups was significant ($p < 0.05$). The mean level of serum IL-2 in 11 patients treated with human leukocyte interferon was higher than the mean value of all melanoma patients (53 U/ml); the small number of patients and variability of the obtained results, however, render the difference statistically insignificant. The results indicate that the decreased in vitro production of IL-2 in malignant melanoma is associated with a decrease in in vivo IL-2 production in comparison with healthy persons.

Key words: melanoma, interleukin-2

Introduction

Solid malignant tumors are frequently accompanied by suppression of cell-mediated immunity and associated with that impaired survival.[1-3] The effects of specific antitumor responses, such as generation of cytotoxic T-cells, activated macrophages, and antitumor antibodies, are probably most relevant to immunologic control by the host. Besides the initial maturation effects of thymic hormones,[4] the most important is the so-called interleukin cascade which represents a sequence of events involving the citokines of monocyte lypmhoid origin helping to drive the cellular response to target antigens. Current studies focus on interleukin-2 (IL-2) which is a glycoprotein produced by activated T lymphocytes.

According to the results of some studies[5] it is known that most antitumor immune reactions, such as proliferation of T helper and cytotoxic cells, NK activity and generation of LAK cells, are IL-2 dependent. Acting on specific IL-2 cell surface receptors, expressed by activated though not resting immune cells, IL-2 stimulates immunity. Though activated T cells, B cells, and macrophages express IL-2 receptors, the most important source of serum IL-2 has still not been clearly explained. Also,

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the results of some studies[6] suggest that serum IL-2 is involved in regulation of some IL-2-dependent immune functions.

The central question is whether IL-2 function is abnormal in patients with solid tumors who commonly exhibit depression of cell-mediated immunity.

Several studies have demonstrated a reduced in vitro IL-2 production after mitogenic stimulation in most patients with metastatic cancer. On account of too low sensitivity of previous assays, little data were available on IL-2 spontaneous in vivo production in cancer patients until recently.[7-9] The development of sensitive ELISA method enabled us to investigate serum IL-2 concentrations in patients with malignant melanoma.

In view of the previously mentioned facts, serum levels of IL-2 were investigated in patients with malignant melanoma in comparison with healthy persons.

Patients and methods

The study included 30 patients with malignant melanoma. There were 12 male and 13 female patients with the mean age 51.4 years (range 31–76 years). Thirty healthy persons (blood donors) served as a control group; there were 15 males and 15 females with the mean age 41 years (range 25–57 years).

In all patients the tumor was histologically proven after surgical removal, and none of them was treated with exogenous recombinant interleukin-2. Disease activity was determined at the time when blood samples were collected. Eleven patients with malignant melanoma were treated intramuscularly with human leukocyte intereferon (2×10^6 U weekly for 30 weeks). The blood samples from those patients were collected throughout the duration of treatment.

Serum interleukin-2 (serum IL-2) levels were measured by means of Inter Test 2 Human IL-2 ELISA test kit (Genzyme-Corporation, Boston, Massachusetts, USA) which is a solid phase enzyme immunoassay employing the multiple antibody sandwich principle.

Results

The mean value (±SE) of serum IL-2 in healthy donors was 269 U/ml (269±66, range 6.9 - 1881 U/ml). In males the mean serum IL-2 value was 259 U/ml and in females 279 U/ml (Table 1). There was no significant sex- and age-related difference in the group of healthy persons. However, since there was a difference between mean age of healthy donors and melanoma patients, the control group was divided into two groups, i.e. persons over 40 and those under 40 years of age. The mean value in healthy donors over 40 years of age was 292 U/ml, while in younger donors it was 249 U/ml; there was no significant impact of age on serum IL-2 levels.

Table 1. Serum interleukin-2 levels in healthy donors according to the sex and age distribution.

Group	No	serum IL-2 Levels AM* ± SE**	Range
Males	15	259	13.8 – 536.2
Females	15	279	11.5 – 1881
Age:			
>40	14	292	13.8 – 1881
<40	16	249	11.5 – 891
All	30	269 ± 66	6.9 – 1881

* AM – arithmetic mean
** SE – standard error

In patients with malignant melanoma the mean value of serum IL-2 was 27±9 U/ml (Table 2); in female patients 28 U/ml and in male patients 26 U/ml. There were no sex-related differences noted in melanoma patients. In older patients (over 51 years) mean serum IL-2 level was 27 U/ml, and in younger patients (under 51 years) this value was nearly the same - 27 U/ml.

Table 2. Serum IL-2 levels in patients with malignant melanoma according to the sex and age distribution.

Group	No	serum IL-2 Levels AM* ± SE**	Range
Males	12	26.1	2 – 127
Females	13	28.4	2 – 200
Age:			
>51	11	27.3	2 – 127
<51	14	27.2	2 – 200
All	25	27.3 ± 9.3	2 – 200

* AM – arithmetic mean
** SE – standard error

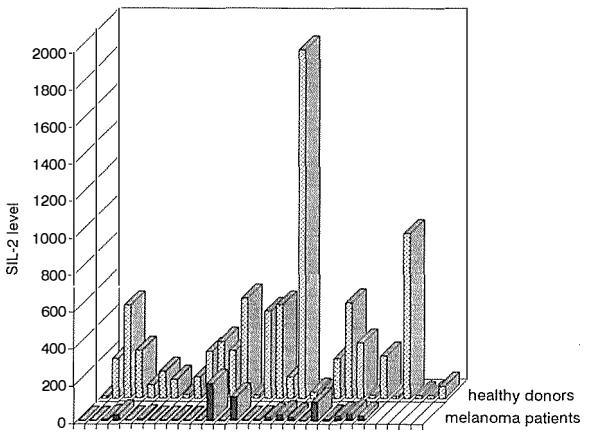

Figure 1. Serum IL-2 levels in healthy donors and melanoma patients.

Serum IL-2 levels in melanoma patients and healthy donors are presented in Figure 1. The difference between mean values of serum IL-2 in melanoma patients and in healthy donors was significant (27±9 U/ml versus 269±66 U/ml, $p<0.05$). In 5 patients the disease was found to have recurred by the time of sample taking. In these patients with recurrence, the mean value was decreased (6.8 U/ml). Despite of a low number of cases, it seems that the extent of disease (or disease activity) influenced the serum IL-2 levels.

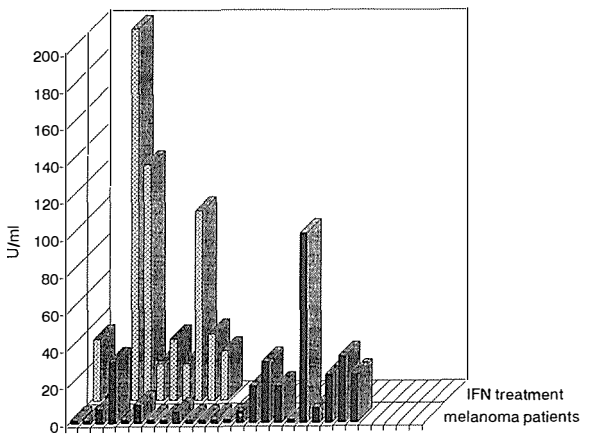

Figure 2. Serum levels in all melanoma patients and 11 patients that were on adjuvant treatment with human leukocyte interferon (2×10^6 units weekly, intramuscular application) after surgical removal of the primary tumor.

At the time of sample taking 11 patients were on adjuvant treatment with human leukocyte interferon (2 × 106 units weekly, intramuscular application) after surgical removal of the primary tumor. In these patients the mean value of serum IL-2 was 57 U/ml (Figure 2), which was higher when compared with otherwise decreased levels of serum IL-2 in melanoma patients. Although, the difference in serum IL-2 levels between all patients and patients treated with human leukocyte interferon was not significant. Also, the serum IL-2 levels were not in the range of the levels of controls employed in this study (i.e. 269 + 66 U/ml).

However, according to our findings it can be postulated that the extent of the disease could influence the serum IL-2 levels since a decrease in serum IL-2 was found in the group of patients with recurrence when compared with the mean serum IL-2 value in all patients (6.8 U/ml versus 27 U/ml).

Discussion

The aim of this study was to assess the potential role of serum IL-2 in the diagnosis and prediction of recurrence in malignant melanoma patients.

Biological significance of altered levels of Il-2 is still not clear; in particular, it is not yet clear whether the increased levels in the blood reflect possible activation of immune cells, or should be ascribed to immune dysfunction.

Although the lymphoproliferative response to mitogens or antigens is frequently depressed in cancer patients, their ability to produce IL-2 by lymphocyte stimulation with PHA appears relatively normal, as reported in literature. However, subgroups with advanced disease did have depressed IL-2 production.[1, 8] Furthermore, in some studies the presence of soluble form of IL-2 receptors was evaluated; increased values were found in patients with small-cell lung carcinoma . Additionally, in breast cancer patients serum IL-2R levels after surgery were significantly higher than those before surgery.[10] The values were found to correlate with the extent of disease.[11]

Decreased serum IL-2 levels in our study are consistent with some other reports, and so is also the finding that further decrease in serum IL-2 levels in our melanoma patients was associated with recurrence of the disease. The influence of human leukocyte interferon could be ascribed to various reasons though it is possible that, with respect to a small number of cases studied, interferon could influence the production of IL-2 in vivo. The increased serum IL-2 levels in patients treated with human leukocyte interferon could also be ascribed to crude extract of interferon containing minor quantities of IL-2.

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