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Recombinant human interleukin-1 beta: new possibilities for the prophylaxis and correction of toxic myelodepression in patients with malignant tumors II. Phase II study of the protective effect of recombinant human interleukin-1 beta on myelodepression induced by chemotherapy in cancer patients

Abstract

The clinical study of human recombinant IL-1beta as a leukopoiesis protector, administered intravenously and subcutaneously, simultaneously with the chemotherapy, confirmed the "protective" effect of this cytokine in patients with grade II leukopenia induced by previous cycles of chemotherapy. The highly protective effect of IL-1beta was proved by the normalization of absolute peripheral blood granulocyte counts over 5 days, from the start of hemostimulation in patients with leukopenia induced by previous cycles of chemotherapy, despite the continuation of cytostatic treatment. Changing the method of IL-1beta administration from the intravenous to the subcutaneous route had no statistically significant effect on the protective influence of IL-1beta. The time taken for complete restoration of leukopoiesis was almost the same for both methods, 5 ± 1 days and 7 ± 1 days for s.c. and i.v. methods respectively. This effect of IL-1beta, not seen in other hematopoietic growth factors such as GM-CSF and G-CSF, allows greater flexibility as regards chemotherapy and provides increased effectiveness of anticancer treatments.

Full text

INTRODUCTION

Cytokines as hematopoiesis stimulators are now widely used in cancer patients for correction of toxic leukopenia induced by combination chemotherapy. Several published papers have been devoted to clinical trials of IL-1 as a stimulator of hematopoiesis in cancer patients undergoing chemotherapy [1-4]. IL-1 induces production of colony-stimulating factors (G-CSF, M-CSF, GM-CSF), IL-3, IL-6 and, cooperatively with these cytokines, directly or indirectly stimulates leukopoiesis *in vivo*, increasing the numbers of myeloid lineage cells [5-7].

According to experimental data, unlike colony-stimulating factors, IL-1 not only restored neutrophil counts after administration of cytostatic agents, but also had a protective effect on hematopoiesis. In animals, IL-1 protected bone marrow polypotent stem cells and early myeloid precursors when injected before radiation or cytostatics (including alkylating) at sublethal and lethal doses [8-

10]. Preliminary clinical data on IL-1 protective activity in phase I trials have been obtained using IL-1 alpha [11].

Our previous data from phase I-II clinical trials of IL-1beta administered to cancer patients after chemotherapy, demonstrate that it has high leukostimulatory activity [12]. In this paper, we report the results of clinical trials where human recombinant IL-1beta has been used for protection of bone marrow hematopoiesis in cancer patients during chemotherapy.

MATERIALS AND METHODS

The human recombinant IL-1beta [13] was produced in the State Research Institute of Highly Pure Biopreparations (St. Petersburg, Russia). Recombinant IL-1beta appeared to be identical to the natural human IL-1beta in terms of its physical, chemical and biological properties [14]. This preparation was approved for clinical use by the Russian Ministry of Health (registration number 97/51/6).

IL-1beta was administered, as a protector of leukopoiesis, for 30-90 min by i.v. drop infusion in 500 ml of isotonic (0.9%) sodium chloride solution at a dose of 15-20 ng/kg daily for 5 days. Paracetamol, noramidopyrin-methansulfonate-natrium, diphenhydramine hydrochloride and chlorpyramine were used to prevent or reduce pyrogenic reactions.

Subcutaneous IL-1beta administration was performed over 10 days according to the following schedule: 100 ng in 1.0 ml of physiological saline on the first day; 200 ng in 2.0 ml of physiological saline on the second day and 300 ng in 3.0 ml of physiological saline on the third day and every day thereafter. The total dose of IL-1beta was 2,700 ng per course.

The protective effect of IL-1beta administered by i.v. drop infusion was evaluated in 36 patients (13 males and 23 females-Group 1). The mean age was 39 years (ranging from 18 to 69 years). Their diagnoses were: Hodgkin's disease, non-Hodgkin's lymphoma and disseminated breast cancer - 21, 14 and 1 patient respectively. The patients in the above-mentioned group demonstrated initial, moderate grade II leukopenia ($M \pm SD = 2.7 \pm 0.2$ **x** 10^9/L), with a minimal leukocyte count (1.1 **x** 10^9/L) that impeded continuation of the chemotherapy. This group of patients received the planned chemotherapy according to the programs LOPP, MOPP, CCNU-OPP, BVM, ABVD, CVAMP, COP-BLAM, CCNU-COP,

simultaneously with IL-1beta that was administered from the first day of administration of the cytostatics.

The protective effect of IL-1beta on leukopoiesis and granulopoiesis with s.c. administration was studied in a group of 16 patients. The mean age was 43 years (ranging from 18 to 63-Group 2), 4 males and 12 females. They were suffering from Hodgkin's disease, non-Hodgkin's lymphoma, advanced breast cancer and carcinoid (7, 5, 3 and 1 patients respectively). All patients in this group had grade II leukopenia (M ± SD = 2.9 ± 0.2 **x** 10^9/L) and grade II moderate neutropenia (M ± SD = 1.8 ± 0.2 **x** 10^9/L) caused by previous chemotherapy (MOPP, LOPP, ABVD, CCNU-COP, CHOEP, VAB, FAC programs). During the study, they received the same cycle of chemotherapy treatment as before. The detailed characteristics of patients by gender, age, diagnoses and details of previous treatment is shown are Table 1.

Informed consent was obtained from all patients.

The reliability of any differences observed during data processing was determined using Student's test and the X-square tests.

RESULTS AND DISCUSSION

*Protective activity of IL-1*beta *administered by intravenous drop infusion*

The previous experimental data on the protective properties of IL-1beta and the first positive clinical results of its leukostimulatory activity obtained by us [12], served as a basis for further study of the possibilities of using human recombinant IL-1beta simultaneously with chemotherapy in patients already displaying leukopenia (< 3.0 **x** 10^9/L), in order to increase the intensity of chemotherapy, and combined chemotherapy and radiotherapy of malignant tumors. The analysis of IL-1beta activity as a leukopoiesis protector was conducted in a group of 36 patients with malignant tumors requiring chemotherapy. In this group of patients, IL-1beta was administered by i.v. drop infusion daily for 5 days at a dose of 15-20 ng/kg.

In this clinical trial, IL-1beta was administered simultaneously with the next combined chemotherapy courses that were given to patients according to their cancer treatment programs, despite existing grade II leukopenia (2.7 ± 0.2 **x**

10^9/L), with a minimal peripheral blood leukocyte count of 1.1 **x** 10^9/L after previous chemotherapy courses.

The protective properties of IL-1beta were confirmed (Table 2) by the increase in the peripheral blood leukocyte count to 4.8 ± 0.4 **x** 10^9/L during administration of the cytokine, despite the simultaneous administration of cytostatics. By the end of cytostatic treatment, there was a decrease in the leukocyte count to 3.9 ± 0.3 **x** 10^9/L ($p < 0.001$), with a maximum leukocyte count of 10.4 **x** 10^9/L. The restoration of the leukocyte count was observed within 7 ± 1 days on average, from the beginning of administration of IL-1beta, *i.e.* within a similar time interval as for the leukopoiesis stimulation after chemotherapy (8 ± 1 days). Apparently this phenomenon may be explained not only by the protective effect but also by concomitant myelopoiesis stimulation.

The rapid and stable increase of the absolute peripheral blood granulocyte counts after administration of IL-1beta (Table 2) from the initial level of 1.6 ± 0.2 **x** 10^9/L to 3.0 ± 0.3 **x** 10^9/L by the end of combined chemotherapy ($p < 0.001$), can be considered evidence of great protective activity. The most significant increase in the absolute granulocyte counts up to 3.9 ± 0.4 **x** 10^9/L was registered during the IL-1beta administration ($p < 0.001$), *i.e.* within 5 days. It must be mentioned that full restoration of the absolute granulocyte count (2.1 ± 0.6 **x** 10^9/L) was recorded in 7 out of 36 patients with the initial leukopenia (1.8 ± 0.2 **x** 10^9/L) and grade III neutropenia (0.6 ± 0.05 **x** 10^9/L), in spite of profound myelodepression that made continuation of anticancer chemotherapy impossible. This restoration allowed the continuation of the planned chemotherapy in these patients.

Protective activity of IL-1beta ***administered by subcutaneous injection***

The protective effect of IL-1beta administered s.c. at rather low doses of 4.5 ng/kg was studied in 16 patients (Table 2) with initial grade II leukopenia (2.9 ± 0.2 **x** 10^9/L) and grade I neutropenia (1.8 ± 0.2 **x** 10^9/L). Within 5 days of starting IL-1beta administration, an increase in the peripheral blood leukocyte counts to a normal value of 4.4 ± 0.6 **x** 10^9/L ($p < 0.02$) was recorded, instead of an expected decrease. The time interval for myelopoiesis restoration was even shorter than that seen with i.v. IL-1beta infusions (5 ± 1 days *versus* 7 ± 1 days), although the difference appeared to be statistically insignificant ($p > 0.1$). At the end of combined chemotherapy or at the end of IL-1beta administration

(depending on the duration of the chemotherapy cycle), only insignificant decreases in leukocyte counts to 3.6 ± 0.6 **x** 10^9/L were registered, while the absolute granulocyte counts (2.8 ± 0.5 **x** 10^9/L) remained at normal levels.

According to the data obtained, the protective effect of IL-1beta is primarily related to the absolute granulocyte count increase (mainly segmented granulocytes). The maximum increase in leukocyte numbers in peripheral blood to 3.1 ± 0.6 **x** 10^9/L ($p < 0.05$) was recorded 5 days after the beginning of IL-1beta administration, and even by the end of therapy, the absolute granulocyte count was above the lower normal value 2.8 ± 0.5 **x** 10^9/L (Table 2). No statistically significant differences were detected between the protective effect of IL-1beta observed following different ways of administration (s.c. and i.v.).

Side effects of recombinant human IL-1beta

The adverse effects of IL-1beta registered after intravenous and subcutaneous administration in these trials appeared to be comparable to the side effects of this cytokine described in other clinical studies [2-4, 15].

The side effects of IL-1beta at doses of 4.5 and 15-20 ng/kg were well tolerated and regressed spontaneously without special treatment and allowed the continuation of treatment with IL-1beta without any limiting toxicity. The most frequent adverse effect during s.c. and i.v. administration of IL-1beta was grade I-III fever in 75 and 66.7% of patients respectively. The fever manifestations were easily resolved by paracetamol tablets or noramidopyrin-methansulfonate-natrium with diphenhydramine hydrochloride injections. During i.v. IL-1beta administration, fever with chills developed in 50% of patients, which were not evident after s.c. IL-1beta administration. IL-1beta administered by i.v. drop infusion at a dose of 15 ng/kg caused a transitory decrease in arterial blood pressure to 100/70 mm in only 1 (2.8%) patient out of 36. This decrease did not require any specific treatment. S.c. injections of IL-1beta were accompanied by moderate local reactions: local hyperemia at the site of injection in 62.5% of patients, soreness at the injection site in 31.2%, fever and chills were less frequent and were shorter in duration. IL-1beta did not cause any clinically registered side effects in 25% of patients receiving it by i.v. drop infusion or in 18.8% of patients receiving it subcutaneously (Table 3).

CONCLUSION

Results obtained show that IL-1beta can be used for protection of bone marrow hematopoiesis when used simultaneously with new cycles of chemotherapy. This property makes the IL-1beta leukostimulatory activity different from that of colony-stimulating factors. It is known that cytokines such as GM-CSF and G-CSF have significant limitations in therapeutic applications because they cannot be used in conjunction with chemotherapy [16]. These preparations can be used no earlier than 24 hours after completion of the chemotherapy course [17]. Moreover, some investigators consider that CSF injections should be started 5 days after the end of chemotherapy because of the possible development of myelotoxicity and damage to haematopoietic cells [18].

According to the results presented here, IL-1beta, unlike colony-stimulating factors, can be used for hematopoiesis protection in conjunction with the next chemotherapy course even in patients with II-III grade neutropenia. In these patients, IL-1beta therapy allows not only protection of bone marrow hematopoiesis from further reductions in the number of granulocytes, but also induces an increase of their numbers in peripheral blood during continuation of chemotherapy. This property of IL-1beta allows us to expand the possibilities of chemotherapy and thus to increase the effectiveness of anticancer treatments.

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Figures

Table 1
Baseline characteristics of patients receiving IL-1β for protection of leukopoiesis during cancer chemotherapy

Baseline characteristics	IL-1β s.c. n = 16	IL-1β i.v. n = 36
ALL patients:	16	36
Males	4	13
Females	12	23
Age (years):		
Mean	43	39
Range	18-63	18-69
Type of disseminated tumor:		
Hodgkin's lymphoma	7	21
Non-Hodgkin's lymphoma	5	14
Breast cancer	3	1
Carcinoid	1	–
Previous treatment:		
Chemotherapy (CT)	9	18
Irradiation + CT	6	16
Surgery + CT	–	1
Surgery	–	1
Immunotherapy + CT	1	–

Table 2
Protective effect of IL-1β on peripheral blood leukocyte and granulocyte counts in patients with initial moderate leukopenia undergoing cancer chemotherapy

Parameters studied	I. IL-1β i.v. (Group 1) (n = 36)	II. IL-1β s.c. (Group 2) (n = 16)	I. IL-1β i.v. (Group 1) (n = 36)	II. IL-1β s.c. (Group 2) (n = 16)
	Leukocytes x 10^9/L (M ± m)		Granulocytes x 10^9/L (M ± m)	
1. Leukocyte count before chemotherapy and administration of IL-1β	2.7 ± 0.2	2.9 ± 0.2 $P_{I,II} > 0.2$	1.6 ± 0.2	1.8 ± 0.2 $P_{I,II} > 0.2$
2. During chemotherapy and administration of IL-1β	4.8 ± 0.4	4.4 ± 0.6 $P_{I,2} < 0.02$ $P_{I,II} > 0.5$	3.9 ± 0.4	3.1 ± 0.6 $P_{I,2} < 0.05$ $P_{I,II} > 0.2$
3. After administration of IL-1β by the end of chemotherapy (in group 1 and 2)/after administration of IL-1β in group 2	3.9 ± 0.3	3.6 ± 0.6 $P_{I,3} > 0.2$ $P_{2,3} > 0.2$ $P_{I,II} > 0.5$	3.0 ± 0.3	2.8 ± 0.5 $P_{I,3} > 0.05$ $P_{I,II} > 0.2$
4. Duration of leukopenia prior to chemotherapy	6 ± 1	8 ± 1 $P_{I,II} > 0.2$	6 ± 1	8 ± 1 $P_{I,II} > 0.2$
5. Restoration interval	7 ± 1	5 ± 1 $P_{I,II} > 0.1$	7 ± 1	5 ± 1 $P_{I,II} > 0.1$

Table 3
Adverse effects of IL-1β administered by intravenous drop infusion or subcutaneous injection

Adverse effects	Intravenous drop infusion (n = 36)	Subcutaneous injection (n = 16)
Hyperthermia	24 (66.7%)	12 (75%)
I grade	15 (41.7%)	8 (50%)
II grade	7 (19.4%)	4 (25%)
III grade	2 (5.6%)	–
IV grade	–	–
Chill	2 (5.6%)	–
Hyperthermia with chill	18 (50%)	–
Headache	3 (8.3%)	–
Giddiness	1 (2.8%)	–
Weakness	1 (2.8%)	–
Nausea	–	–
Vomiting	–	–
Phlebitis	2 (5.6%)	–
Blood pressure decrease	1 (2.8%)	–
Arthralgia	–	–
Hyperemia at the site of injection	–	10 (62.5%)
Local pain at the site of injection	–	5 (31.2%)
Without complications	9 (25%)	3 (18.8%)

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