

Volume 12, issue 4, December 2001 | Articles originaux

Recombinant human interleukin-1 beta: new possibilities for the prophylaxis and correction of toxic myelodepression in patients with malignant tumors I. Phase I-II clinical trials of recombinant human interleukin-1 beta as a leukopoiesis stimulator in cancer patients receiving combination chemotherapy

Abstract

Human recombinant interleukin-1 beta (IL-1beta), administered by intravenous drop infusion, at doses of 10-20 ng/kg daily over 5 days, to a group of 67 patients suffering from malignant tumors and with grade II-IV toxic leukopenia, caused an increase in the leukocyte count to the normal value, within, on average, 8 ± 1 days. The leukostimulatory effect of IL-1beta, administered subcutaneously at an average dose of 4.6 ± 0.3 ng/kg (n = 16), appeared to be almost equal to that found for intravenous drop infusion at a dose of 10-20 ng/kg (n = 67). In patients receiving subcutaneous IL-1beta injections, the peripheral blood total leukocyte and granulocyte counts achieved normal values within 9 days. The side effects of IL-1beta at a dose of 0.1-20.0 ng/kg were well tolerated.

Full text

INTRODUCTION

The limiting toxicity of the majority of cytostatic drugs used in the chemotherapy of malignant tumors reveals itself as development of myelodepression, primarily leukopenia, caused by a decrease in the neutrophil count. Toxic myelodepression impedes the continuation chemotherapy at the necessary intensity and intervals planned, with the result that the therapeutic effect is reduced. Several growth factors (different colony-stimulating factors, IL-1, IL-3, IL-6, IL-11, TPO and others) have been studied in animal experiments and clinical trials, to identify any bone marrow reconstitution following chemotherapy. Of these, only colony-stimulating factor (CSF) has been successfully introduced into clinical practice.

IL-1 is one of the main mediators of the development of host defense reactions to invading pathogens [1, 2]. The important component of IL-1's versatile biological activity is its ability to stimulate hematopoiesis. IL-1-induced hematopoiesis stimulation is expressed as an increase in the numbers of neutrophils, lymphocytes, eosinophils, and, to some extent, platelets, due to induction of thrombocyte growth factor synthesis [3-5]. 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 stimulate leukopoiesis *in vivo*, increasing subpopulations of premature myeloid line cells [6-10]. IL-

1alpha and IL-1beta restore the neutrophil count in animals after administration of 5-fluorouracil [7, 11], cyclophosphamide [12-14], and doxorubicin [15].

Both members of the IL-1 family (IL-1alpha and IL-1beta) have been studied in several clinical trials, for the reconstitution of bone marrow in cancer patients after high dose chemotherapy, and have been shown to have dose-dependent leukostimulatory activity [16-22]. Unfortunately, at very high doses (100-200 ng/kg)
IL-1 induced several adverse effects, including hypotonia, and almost 30% of patients needed particular treatment for these [23-26]. Bearing in mind that IL-1 has a great capacity for stimulating bone marrow hematopoiesis, we decided to investigate its leukostimulatory activity under different regimens and administration routes, at relatively low doses. In this paper, we report the results of clinical trials where human recombinant IL-1beta was used for reconstitution of bone marrow after chemotherapy in cancer patients.

MATERIALS AND METHODS

The human recombinant IL-1beta [27] was produced in the State Research Institute of Highly Pure Biopreparations (St. Petersburg, Russia). The recombinant
IL-1beta appeared to be identical to the natural human IL-1beta in terms of its physical, chemical and biological properties [28]. This preparation was approved for clinical use by the Russian Ministry of Health (registration number 97/51/6).

IL-1beta was administered as a stimulator of leukopoiesis over 30-90 min by i.v. drop infusion in 500 ml of isotonic (0.9%) sodium chloride solution, at a dose of 10-20 ng/kg daily for 5 days. Paracetamol, noramidopyrin-methansulfonate-natrium, diphenhydramine hydrochloride and chlorpyramine were used in some patients 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.

Clinical study of human recombinant IL-1beta as a stimulator of leukopoiesis was conducted at the N.N. Petrov Research Institute of Oncology (St. Petersburg), in a group of 93 patients with morphologically verified, disseminated forms of solid tumors and malignant lymphomas, who were receiving combined chemotherapy. Clinical trials were started in phase I studies, with escalating doses of IL-1beta administered by i.v. drop infusion in 23 patients (6 males and 17 females, age range from 17 to 67 years, average - 42 years). IL-1beta doses were as follows: 0.1-0.4 ng/kg (6 patients), 0.5-1.2 (2 patients), 1.6-4.0 (6 patients), 4.5-10.0 (9 patients). Among these patients 16 were with disseminated melanoma, 3 with breast cancer, 2 with Hodgkin's disease, 1 with lung cancer and 1 with Ewing's sarcoma.

The activity of IL-1beta as a stimulator of leukopoiesis was studied in a group of 67 patients (17 males and 50 females) (group A). The mean age was 41 years (ranging from 17 to 69 years). These patients received IL-1beta by intravenous drop infusion. The patients were suffering from generalized forms of Hodgkin's disease (38 patients), non-Hodgkin's lymphomas (18 patients) and solid tumors (11 patients). Fifty-one patients out of 67 (76%) had grade III and IV leukopenia (according to WHO criteria, 1979), and 16 patients (24%) had grade IV toxic leukopenia with decreased peripheral blood leukocyte numbers ($M \pm m = 1.5 \pm 0.1$ **x** 10^9/L). Leukopenia was caused by repeated standard cycles of combined chemotherapy according to programs MOPP, CCNU-OPP, ABVD, DOPP-ABV, BEACOPP, BMV, EVAP, CHOP, CCNU-COP, CVAMP, CHOEP, CAF, DBCT. In 9 patients (13%), myelodepression had been induced by prior, combined chemotherapy and radiation therapy.

The leukostimulatory effect of human recombinant IL-1beta on s.c. administration was studied in a group of 16 patients (5 males and 11 females). Their mean age was 39 years (ranging from 23 to 68). They were suffering from Hodgkin's disease (7 patients), non-Hodgkin's lymphomas (5 patients), disseminated breast cancer (3 patients), teratoblastoma (1 patient). All patients had grade II-III leukopenia ($M \pm SD = 1.6 \pm 0.2$ **x** 10^9/L) and neutropenia ($M \pm m = 0.9 \pm 0.1$ **x** 10^9/L) caused by combination chemotherapy according to the programs MOPP, LOPP, ELOP, CVAMP, CHOP, CCNU-COP, CMP, ACE and combined chemotherapy and radiation therapy.

The results obtained have been compared to another similar group (group C) of patients ("historical" control group), consisting of 30 patients (4 males and 26

females). The mean age was 40 years (ranging from 16 to 64), and they were not receiving any leukostimulatory treatment. They were suffering from non-Hodgkin's lymphoma, Hodgkin's disease and breast carcinoma - 11, 17 and 2 patients respectively. All patients of this group had grade III toxic leukopenia caused by combined chemotherapy and, in some cases, by chemotherapy and radiation therapy. The detailed characteristics of patients by gender, age, diagnoses and details of previous treatment are shown in Table 1.

In addition, a comparative pilot study of the leukopoiesis stimulatory effect of GM-CSF (Leucomax) and IL-1beta was conducted. Twenty patients were enrolled in this study (4 males and 16 females). Their mean age was 42 ± 3.5 years (ranging from 21 to 69). These patients were suffering from Hodgkin's disease and non-Hodgkin's lymphoma (12 and 8 respectively). All patients had grade III and IV leukopenia (according to WHO criteria, 1979).

Initial leukopenia before the administration of leukostimulants was at 1.2 ± 0.1 **x** 10^9/L in group L receiving Leucomax, and 1.4 ± 0.1 **x** 10^9/L in group I receiving IL-1beta. Initial absolute granulocyte counts in peripheral blood were 0.6 ± 0.1 **x** 10^9/L and 0.7 ± 0.1 **x** 10^9/L respectively. Myelosuppression was caused by several programs of combined chemotherapy (MOPP, CVAMP, CCNU-OPP, CHOP, CHOEP, BACOD-E). Leucomax was administered s.c. at a dose of 5 mkg/kg daily for 5 days. IL-1beta was administered by i.v. drop infusion at a dose of 15 ng/kg in 500 ml of physiological saline once a day for 5 days. The effectiveness of hemostimulation was determined by the leukocyte count and absolute granulocyte count dynamic in peripheral blood, and by the time taken for their restoration to normal levels.

Informed consent was obtained from all patients.

The reliability of any differences observed during data processing was determined using Student's test,
C-square and Wilkinson-Mann-Whitney test.

RESULTS AND DISCUSSION

*Leukostimulatory activity of human recombinant IL-1*beta *administered by intravenous drop infusion*

The leukostimulatory effect of recombinant human IL-1beta administered by i.v. drop infusion was studied and confirmed in patients with grade III and IV toxic leukopenia. Study group A consisted of 67 patients with disseminated forms of malignant lymphoma and solid tumors; the great majority of them (76%) had profound grade III and IV leukopenia. The leukocyte counts in peripheral blood of patients in group A after chemotherapy but before administration of IL-1beta was 1.5 ± 0.1 **x** 10^9/L, with a minimum level of 0.3 **x** 10^9/L. The leukopenia in these patients, confirmed by repeated investigation, had continued for 8 ± 1 days (with a maximum of 60 days), prior to administration of the cytokine.

The administration of IL-1beta at doses of 10-20 ng/kg caused an increase in leukocyte levels to 4.7 ± 0.3 **x** 10^9/L over 8 ± 1 days, starting from the first administration. The leukostimulatory effect of IL-1beta was registered from day 3 to day 5 of its administration and was confirmed by statistically significant ($p > 0.001$) leukocyte count increases up to 3.4 ± 0.3 **x** 10^9/L (see Table 2).

The same changes were seen in the absolute granulocyte count restoration in peripheral blood of group A patients (see Table 2). The granulocyte counts increased to 3.2 ± 0.2 **x** 10^9/L within 8 ± 1 days after the first administration of IL-1beta ($p < 0.001$), while the initial granulocytopenia had been 0.9 ± 0.1 **x** 10^9/L. The absolute peripheral blood granulocyte count restoration to normal levels of 2.3 ± 0.1 **x** 10^9/L on average (increment equal to 256 ± 50%) was observed even during IL-1beta administration, *i.e.* within a short time frame.

This considerable effect of IL-1beta administration was not registered in 7 patients with malignant lymphoma with specific liver damage, nor in 9 patients who had undergone combined chemotherapy and radiation treatment (all of them in group A). These patients displayed longer period of leukopoiesis restoration lasting up to 27-32 days. However, 9 patients with malignant lymphoma and specific bone marrow damage without blast transformation, had no statistical differences compared to group A for all parameters.

The study did not reveal any statistical difference between the therapeutic effect of IL-1beta at doses ranging from 10 to 20 ng/kg. The dose of 15 ng/kg was therefore selected as effective.

The patients in group A were divided into three subgroups, depending on the degree of bone marrow suppression, for the differential analysis of the

therapeutic effect of IL-1beta. There were 16 patients with grade II leukopenia prior to leukostimulation (the peripheral blood leukocyte count was 2.4 ± 0.1 **x** 10^9/L) in the first subgroup, 38 patients with grade III leukopenia (1.4 ± 0.1 **x** 10^9/L) in the second subgroup, and 13 patients with grade IV leukopenia (0.7 ± 0.1 **x** 10^9/L) in the third group. The complete peripheral blood leukocyte counts and absolute granulocyte count restoration were registered in all subgroups. The leukocyte counts in these subgroups of patients reached 5.0 ± 0.4 **x** 10^9/L, 4.4 ± 0.3 **x** 10^9/L, 5.2 ± 1.4 **x** 10^9/L, and absolute granulocyte counts reached 2.9 ± 0.4 **x** 10^9/L, 3.0 ± 0.2 **x** 10^9/L, 4.4 ± 1.3 **x** 10^9/L in the first, second and third subgroups, respectively, without statistically significant differences between the subgroups ($p > 0.05$). However, the most rapid restoration of leukopoiesis was recorded in patients with initial grade II leukopenia already during IL-1beta administration (M ± m = 5 ± 1 days), and the longest leukopoiesis restoration period (M ± m = 12 ± 1 days) was registered in patients with the most profound initial myelopoiesis suppression (grade IV leukopenia, $p < 0.001$).

The leukostimulatory effect of IL-1beta in group A was compared to in the control group C of 30 patients with toxic grade III leukopenia who had independent (spontaneous) myelopoiesis restoration without additional administration of leukostimulants. The statistical analysis conducted in both groups revealed statistically significant ($p < 0.001$), 3-fold more rapid leukopoiesis restoration after stimulation with IL-1beta in group A as compared with group C (see Table 2). Patients in group A, who had been receiving IL-1beta, appeared to have total peripheral blood leukocyte count restoration prior to the next chemotherapy treatment course (M ± m = 8 ± 1 days) while patients in group C achieved the same result in 25 ± 2 days.

*Leukostimulatory activity of human recombinant IL-1*beta *administered by subcutaneous injection*

One of the most important aspects of the study was the investigation of the therapeutic effect of IL-1beta after changing the way of administration from i.v. to s.c. for the purpose of extending the cytokine administration under out-patient conditions and reduction of side effects. In this set of clinical trials, the group of 16 patients with malignant lymphoma and solid tumors received IL-1beta s.c. at a total dose of 2,700 ng per course.

A statistically significant ($p < 0.001$) increase in peripheral blood leukocyte counts from 1.6 ± 0.2 **x** 10^9/L to 5.5 ± 0.5 **x** 10^9/L in 9 ± 1 days was found in this group of patients, which demonstrated almost complete (up to 92%) leukocyte count restoration. The initial level (prior to chemotherapy) in these patients was 6.0 ± 0.8 **x** 10^9/L. A significant leukocyte count increase ($p < 0.001$) by 219% on average, up to 3.5 ± 0.4 **x** 10^9/L was shown within 3-5 days from the start of s.c. IL-1beta administration, and, more importantly, the absolute peripheral blood granulocyte counts were restored to normal levels ($M \pm m = 2.2 \pm 0.4$ **x** 10^9/L) at the same time (Table 2).

The granulocyte counts (see Table 2) fluctuated between 0.9 ± 0.1 **x** 10^9/L as the initial level of neutropenia and 3.7 ± 0.4 **x** 10^9/L after 9-10 days of IL-1beta administration ($p < 0.001$). The granulocyte count after IL-1beta administration was not statistically different in absolute values from the initial level ($M \pm SD = 4.6 \pm 0.7$ **x** 10^9/L) before chemotherapy ($p > 0.2$).

The data on the therapeutic effect of IL-1beta after s.c. administration in a group of 16 patients are shown in Tables 3 and 4. The previous specific chemotherapy treatment had induced grade II (2.5 **x** 10^9/L), grade III (1.4 **x** 10^9/L) and grade IV (0.7 **x** 10^9/L) toxic leukopenia in 5, 7 and 4 patients of this group respectively. The therapeutic effect of IL-1beta administered s.c. was registered in all patients, independent of the level of bone marrow suppression. These patients demonstrated complete restoration of the peripheral blood leukocyte count to 5.4 ± 1.0 **x** 10^9/L, 5.0 ± 0.9 **x** 10^9/L, 6.5 ± 0.7 **x** 10^9/L and restoration of absolute granulocyte counts to 3.4 ± 0.7 **x** 10^9/L, 3.6 ± 0.7 **x** 10^9/L, 4.3 ± 1.0 **x** 10^9/L respectively. There were no statistically difference between the subgroups after leukopoiesis stimulation. The time periods of the bone marrow restoration in the subgroups were similar ($p > 0.05$). It is important to mention that patients with grade II and IV leukopenia demonstrated a complete leukocyte count restoration to normal levels in the same period of time: 7 ± 1.5 and 8 ± 1 days respectively.

It is also important to note that the effect of IL-1beta after s.c. administration was obvious even in patients with grade IV leukopenia and neutropenia caused by previous combination chemotherapy (4 patients out of 16). In these patients, the initial peripheral blood leukocyte counts were 0.7 ± 0.1 **x** 10^9/L and the absolute granulocyte counts were 0.2 ± 0.1 **x** 10^9/L. During the 5 days of IL-1beta administration, we observed a stable increase in leukocyte counts up to 3.9 ± 0.9 **x** 10^9/L and granulocyte counts to 1.5 ± 0.9 **x** 10^9/L. After the course,

complete restoration of the leukocyte counts to 6.5 ± 0.7 **x** 10^9/L and granulocyte counts to 4.3 ± 0.1 **x** 10^9/L was registered.

The results presented (Table 2) allow us to compare the IL-1beta leukostimulatory effect in patients receiving IL-1beta s.c. as a single dose of 4.3 ± 0.3 ng/kg (n = 16) and i.v. drop infusions at a dose of 10-20 ng/kg of (n = 67). They also allow us to compare the results obtained from the patients in the "historical" control group who had spontaneous restoration of leukopoiesis (without hemostimulation). The therapeutic effect of IL-1beta administered subcutaneously, manifested itself similarly to that in patients receiving i.v. drop infusions of the drug. Myelopoiesis restoration in the s.c. and i.v. groups was observed within a very similar time interval i.e. 8 ± 1 and 9 ± 1 days ($p > 0.2$) from the beginning of hemostimulation, respectively. The leukocyte and granulocyte counts reached a normal level to 4.7 ± 0.3 **x** 10^9/L and to 3.2 ± 0.2 **x** 10^9/L respectively after i.v. drop infusions of the cytokine. The leukocyte and granulocyte counts increased to 5.5 ± 0.5 **x** 10^9/L and 3.7 ± 0.4 **x** 10^9/L respectively after s.c. administration. There was no statistical difference between i.v. and s.c. IL-1beta administration. The great leukostimulatory effect of subcutaneously administered IL-1beta was seen despite the lower single dose (4.6 ± 0.3 ng/kg) and total (2,700 ng) doses, as compared to the i.v. drop infusions of the cytokine.

*The comparative analysis of the leukostimulatory effect of Leucomax (Molgramostim) and recombinant IL-1*beta *in patients with malignant lymphoma and myelodepression induced by administration of cytostatics (pilot study data)*

The comparative analysis of the leukostimulatory effect of the GM-CSF preparation - Leucomax (molgramostim) and recombinant IL-1beta was conducted as an open, randomized clinical pilot phase III study in 20 patients with malignant lymphoma and with grade III and IV leukopenia caused by combined chemotherapy. The leukopenia level prior to administration of hematopoiesis stimulators was on average 1.2 ± 0.1 **x** 10^9/L in group L, receiving Leucomax (10 patients), and 1.4 ± 0.1 **x** 10^9/L in group I, receiving IL-1beta (10 patients). The initial numbers of peripheral blood granulocytes were 0.6 ± 0.1 **x** 10^9/L and 0.7 ± 0.1 **x** 10^9/L respectively ($p_U > 0.05$). Myelosuppression continued for 5.5 ± 2.5 days on average in group L and 4 ± 2 days in group I ($p_U > 0.05$) and

was caused by a variety of chemotherapy programs (MOPP, CVAMP, CCNU-OPP, CHOP, CHOEP, BACOD-E).

The peripheral blood leukocyte counts increased from 1.2 ± 0.1 **x** 10^9/L prior to administration of Leucomax, to 7.8 ± 2.6 **x** 10^9/L after the end of its administration ($p_u < 0.001$), the level of leukocytes reached the normal value (4.8 ± 1.2 **x** 10^9/L) during the leukostimulation treatment. The absolute peripheral blood granulocyte numbers also were rising from 3.2 ± 0.9 **x** 10^9/L ($p_u < 0.001$) before Leucomax administration and reached 5.6 ± 2.1 **x** 10^9/L ($p_u < 0.001$) after its termination, *i.e.* a nearly complete restoration of absolute granulocyte counts compared to the initial level before chemotherapy (6.2 ± 1.1 **x** 10^9/L $p_u > 0.05$).

Very similar results were obtained in the second group (I) receiving IL-1beta as a leukopoiesis stimulator. IL-1beta caused an increase in the leukocyte counts in peripheral blood from 1.4 ± 0.1 **x** 10^9/L to 4.2 ± 0.5 **x** 10^9/L that reached the normal value within 8 ± 1 days, *i.e.* the same as in group L ($p_u > 0.05$).

Some differences between mean values of leukocyte counts (7.8 ± 2.6 **x** 10^9/L *versus* 4.2 ± 0.5 **x** 10^9/L) after leukopoiesis stimulation in both groups turned out to be not significant according to the Wilkinson-Mann-Whitney criterion and were very likely linked to the ability of Leucomax to cause hyper-stimulation of leukopoiesis. As in group L, the granulocyte level was restored to the normal value 2.4 ± 0.6 **x** 10^9/L during the administration of IL-1beta. The absolute count was to 3.0 ± 0.4 **x** 10^9/L after stimulation, and the differences between the initial level before chemotherapy and final values were not significant ($p_U > 0.05$).

All patients were examined for cortisol levels prior to administration of cytokines, and on day 7 after the start of leukostimulation with Leucomax and IL-1beta. The cortisol levels before and after administration of cytokines changed from 702 ± 117 nmol/L to 665 ± 99 nmol/L and from 647 ± 95 nmol/L to 781 ± 89 nmol/L respectively in groups L and I ($p_U > 0.05$). According to the data obtained, Leucomax and IL-1beta at the doses used, did not induce significant changes in corticosteroid production. Also, neither preparation induced changes in peripheral blood neutrophil functional activity: phagocytosis and oxygen radical production (data not shown).

Both Leucomax and IL-1beta, at the doses used, were well tolerated by the patients. The distinctive and characteristic feature of IL-1beta treatment was

moderate fever, in 80% of patients in group I. The other side effects were not important. Preliminary results indicate that Leucomax and IL-1beta are probably similar as regards their leukostimulatory effects when administered during combined chemotherapy for malignant lymphoma, and that they do not increase corticosteroid levels.

Side effects of recombinant human IL-1beta

IL-1beta at doses of 0.1-20 ng/kg (including phase I studies) were well tolerated, the side effects regressed spontaneously without special treatment, and allowed leukostimulatory or protective treatment with IL-1beta to be continued without limiting toxicity (Table 5). IL-1beta administered i.v. at doses of 0.1-1.2 ng/kg did not cause any side effect. The most frequent adverse effect during administration of IL-1beta at the higher therapeutic doses administered by i.v. drop infusions and s.c., was grade I-III fever in 67.9 and 62.5% of patients respectively ($p < 0.05$). The fever manifestations were easily reduced by paracetamol tablets or noramidopyrin-methansulfonate-natrium with diphenhydramine hydrochloride injections. The grade I hyperthermia (43.8%) was registered more frequently in patients receiving IL-1beta s.c. than in those receiving it i.v. (26.9%), grade II hyperthermia was registered more rarely - 18.8% and 35.9% respectively ($p > 0.05$).

IL-1beta administered by i.v. drop infusion at a single dose of 15 ng/kg IL-1beta caused a transitory decrease in arterial blood pressure to 100/70 mm in only 1 patient. This decrease did not require any specific treatment. S.c. injections of IL-1beta were accompanied by moderate local reactions: hyperemia in 31.2% of patients, soreness at the injection site in 25.0%, fever and chill were less severe and were of shorter duration. IL-1beta did not cause any clinically side effects in 20.5% of patients receiving i.v. drop infusion or in 18.8% of patients receiving s.c IL-1beta.

CONCLUSION

The clinical data obtained suggest that IL-1beta is an effective leukopoiesis stimulator in patients with myelodepression receiving combined chemotherapy, and combined chemotherapy plus radiation treatment for malignant tumors. The ability of human recombinant IL-1beta to re-establish bone marrow

hematopoiesis after chemotherapy has been shown previously in other clinical studies [16, 17, 19].

The subcutaneous route of administration of IL-1beta seems to be the rational and optimal route from the point of view of simplicity and convenience of administration, without the loss of leukostimulatory and protective effects in cancer patients requiring intensive combined chemotherapy and radiation treatment. It is particularly appropriate for out-patient clinics.

A study of the therapeutic effects of higher doses of subcutaneously administered IL-1beta (10-15-20 ng/kg) is planned in the light of the minimal side effects and the possibility of increasing the leukostimulatory and protective effects of this drug.

Acknowledgements. We would like to thank the medical staff of the Chemotherapy Department, N.N. Petrov Research Institute of Oncology, St. Petersburg who helped us with the enrollment of patients and with the clinical study.

References

1. Dinarello C A. 1994. The biological properties of interleu-kin-1. (Review) *Eur. Cytokine Netw.* 5: 517.

2. Roux-Lombard P. 1998. The interleukin-1 family. (Review) *Eur. Cytokine Netw.* 9: 565.

3. Morrissey P, Charrier K, Bressler L, Alpert A. 1988. The influence of IL-1 treatment of the reconstitution of the hemopoietic and immune systems after sublethal radiation. *J. Immunol.* 140: 4204.

4. Castelli M P, Black P L, Schneider M, Pennigton R, Abe F, Talmadje J E. 1988. Protective, restorative and therapeutic properties of recombinant human IL-1 in rodents models. *J. Immunol.* 140: 3830.

5. Kovacs C J, Powell D S, Evans M J, Thomas-Patterson D, Johnke R M. 1996. Enhanced platelet recovery in myelosuppressed mice treated with interleukin-1

and macrophage colony-stimulating factor: potential interaction with cytokines having megakaryocyte colony-stimulating activity. *J. Interferon Cytokine Res.* 16: 187.

6. Hestdal K, Jacobsen S E, Ruscetti F W, Dubois C M, Longo D L, Chizzonite R, Oppenheim J J, Keller J R. 1992. *In vivo* effect of interleukin-1 alpha on hematopoiesis: role of colony-stimulating factor receptor modulation. *Blood* 80: 2486.

7. Moore M A, Warren D J. 1987. Synergy of interleukin-1 and granulocyte colony-stimulating factor: *in vivo* stimulation of stem-cell recovery and hematopoietic regeneration following 5-fluorouracil treatment of mice. *Proc. Natl. Acad. Sci. USA* 84: 7134.

8. Cavaillon J M, Vidard L, Boudaly S, Fitting C, Cohen L, Seman M, David B. 1990. Induction of interleukin-3 by interleukin-1 in the absence of other exogenous stimuli. *Cell. Immunol.* 129: 176.

9. Kovacs C J, Evans M J, Daly B M, Thomas-Patterson D, Johnke R M, Powell D S. 1997. Secondary cytokines interact in sequence with interleukin-1 alpha (IL-1alpha) with or without macrophage colony-stimulating factor (M-CSF) to further accelerate granulopoietic recovery in myelosuppressed animals. *J. Interferon Cytokine Res.* 17: 453.

10. Kennedy S M, Borch RF. 1999. IL-1 beta mediates diethyldithiocarbamate-induced granulocyte colony-stimulating factor production and hematopoiesis. *Exp. Hematol.* 27: 210.

11. Moore M A, Stolfi R L, Martin D S. 1990. Hematologic effect of interleukin-1 beta, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor in tumor-bearing mice treated with 5-fluorouracil. *J. Natl. Cancer Inst.* 82: 1031.

12. Futami H, Jansen R, MacPhee M J, Keller J, McCormick K, Longo D L, Oppenheim J J, Ruscetti F W, Wiltrout R H. 1990. Chemoprotective effects of recombinant human IL-1 alpha in cyclophosphamide-treated normal and tumor-bearing mice. Protection from acute toxicity, hematologic effects, development of late mortality and enhanced therapeutic efficacy. *J. Immunol.* 145: 4121.

13. Hornung R L, Longo D L. 1992. Hematopoietic stem cell depletion by restorative growth factor regimen during repeated high-dose cyclophosphamide therapy. *Blood* 80: 77.

14. Stork L, Barczuk L, Kissinger M, Robinson W. 1989. Interleukin-1 accelerates murine granulocyte recovery following treatment with cyclophosphamide. *Blood* 73: 938.

15. Eppstein D A, Kurahara C G, Bruno N A, Terreli T G. 1989. Prevention of doxorubicin-induced hematotoxicity in mice by interleukin-1. *Cancer Res.* 49: 3955.

16. Iizumi T, Sato S, Iiyama T, Hata R, Amemiya H, Tomomasa H, Yazaki T, Umeda T. 1991. Recombinant human interleukin-1 beta analogue as a regulator of hematopoiesis in patients receiving chemotherapy for urogenital cancers. *Cancer* 68: 1520.

17. Crown J, Jakubowsky A, Kemeny N, Gordon M, Gasparetto C, Wong G, Sheridan C, Toner G, Meisemberg B, Botet J, *et al.* 1991. A phase I trial of human recombinant interleukin-1 beta alone and in combination with myelosuppressive doses of 5-fluorouracil in patients with gastrointestinal cancer. *Blood* 78: 1420.

18. Smith J W 2nd, Longo D L, Alword W G, Janik J E, Sharfman W H, Gause B L, Curti B D, Creekmore S P, Holmlun J T, Fenton R G, *et al.* 1993. The effects of treatment with interleukin-1 alpha on platelets recovery after high dose carboplatin. *N. Engl. J. Med.* 328: 756.

19. Tanaka S, Tabuchi S, Watanabe K, Takigawa H, Akatsuka K, Numata H, Hokama Y, Hori T. 1992. Preventive effects of interleukin-1 beta for ACNU-induced myelosuppression in malignant brain tumors. The experimental and preliminary studies. *J. Neurooncol.* 14: 159.

20. Nemunaitis J, Appelbaum F R, Lilleby K, Buhles W C, Rosenfeld C, Zeigler Z R, Shadduck R K, Singer Y W, Meyer W, Buckner C D. 1994. Phase I study of recombinant interleukin-1 beta in patients undergoing autologous bone marrow transplant for acute myelogenous leukemia. *Blood* 83: 3473.

21. Elkordy M, Crump M, Vrevenburgh J J, Petros W P, Hussein A, Rubin P, Ross M, Gilbert C, Modlin C, Meissenberg B, Coniglio D, Rabinowitz J, Laughlin M, Kurtzberg J, Peters W P. 1997. A phase I trial of recombinant human interleukin-1 beta (OCT-43) following high-dose chemotherapy and autologous bone marrow transplantation. *Bone Marrow Transplant.* 19: 315.

22. Kovacs C J, Kerr J A, Daly B M, Evans M J, Johnke R H. 1998. Interleukin-1 (IL-1) alpha and macrophage colony-stimulating factor (M-CSF) accelerate recovery from multiple drug-induced myelosuppression. *Anticancer Res.* 18: 1805.

23. Weisdorf D, Katsanis E, Verfaillie C, Ramsay N K, Haake R, Garrison L, Blazar B R. 1994. Interleukin-1 alpha administered after autologous transplantation: a phase I/II clinical trial. *Blood* 84: 2044.

24. Rinehart J, Hersh E, Issel B, Triozzi P, Buhles W, Neidhart J. 1997. Phase I trial of recombinant human interleukin-1 beta (rh IL-1 betat), carboplatin, and etaposide in patients with solid cancers: Southwest Oncology Group Study 8940. *Cancer Invest.* 15: 403.

25. Janik J E, Miller L L, Longo D L, Powers G C, Urba W J, Kopp W C, Gause B L, Curti B D, Fenton R G, Oppenheim J J, Conlon K C, Holmlund J T, Sznol M, Sharfman W H, Steis R G, Creekmore S P, Alvord W G, Beauchamp A E, Smith J W 2nd. 1996. Phase II trial of interleukin-1 alpha and indomethacin in treatment of metastatic melanoma. *J. Natl. Cancer Inst.* 88: 44.

26. Rosenthal M A, Dennis D, Liebes L, Furmanski P, Caron D, Garrison L, Wiprovnick J, Peace D, Oratz R, Speyer J, Chachoua A. 1998. Biologic activity of interleukin-1 alpha in patients with refractory malignancies. *J. Immunother.* 21: 371.

27. Kotenko S V, Bulenkov M T, Veyko V P, Epishin S M, Lomakin I B. 1989. Cloning of cDNA encoding human prointerleukin-1 alpha and prointerleukin-1 beta. Proceedings of the USSR academy of sciences, 309: 1005.

28. Ketlinsky S A, Simbirtsev A S, Poltorak A N, Protasov E A, Solovieva L A, Putchkova G V, Konusova V G, Pigareva N V, Kalinina N M, Perumov N D. 1991. Purification and characterization of the immunostimulatory properties of recombinant human interleukin-1 beta. *Eur. Cytokine Netw.* 2: 17.

Figures

Table 1
Baseline characteristics of patients with toxic leukopenia (neutropenia) treated with IL-1β to stimulate leukopoiesis

Baseline characteristics	IL-1β i.v. (n = 67)	IL-1β s.c. (n = 16)	Control group (n = 30)
All patients:	67	16	30
Males	17	5	4
Females	50	11	26
Age (years):			
Mean	41	39	40
Range	17-69	23-68	16-64
Type of disseminated tumor:			
Hodgkin's lymphoma	38	7	17
Non-Hodgkin's lymphoma	18	5	11
Breast cancer	10	3	2
Malignant melanoma	1	–	–
Teratoblastoma	–	1	–
Previous treatment:			
Chemotherapy	57	14	28
Surgery	10	2	2
Leukocytes (x 10^9/L) Before IL-1β:			
Mean (M ± m)	1.5 ± 0.1	1.6 ± 0.2	1.9 ± 0.2
Range	0.5-2.8	0.4-2.8	0.8-2.8
Neutrophils (x 10^9/L) Before IL-1β:			
Mean (M ± m)	0.9 ± 0.1	0.9 ± 0.1	1.1 ± 0.1
Range	0.1-1.6	0.1-1.6	0.5-1.6

Table 2
Dynamics of peripheral blood leucocyte and granulocyte counts following IL-1β administration in patients with myelodepression caused by combined chemotherapy or radiation therapy

Parameters studied	Group A IL-1β i.v. (n = 67)	Group B IL-1β s.c. (n = 16)	Group C Control group (n = 30)	Group A IL-1β i.v. (n = 67)	Group B IL-1β s.c. (n = 16)	Group C Control group (n = 30)
	Leukocytes x 10⁹/L (M ± m)			Granulocytes x 10⁹/L (M ± m)		
1. Initial counts before chemotherapy	5.8 ± 0.5 $P_{A,B} > 0.5$	6.0 ± 0.8	5.8 ± 0.6 $P_{B,C} > 0.5$	3.9 ± 0.4 $P_{A,B} > 0.2$	4.6 ± 0.7	4.2 ± 0.6 $P_{B,C} > 0.5$
2. Leukopenia	1.5 ± 0.1 $P_{A,B} > 0.5$	1.6 ± 0.2 $P_{1,2} < 0.001$	1.9 ± 0.2 $P_{B,C} > 0.2$	0.9 ± 0.1 $P_{A,B} > 0.5$	0.9 ± 0.1 $P_{1,2} < 0.001$	1.1 ± 0.1 $P_{B,C} > 0.1$
3. 3-5 days after the first injection of IL-1β	3.4 ± 0.3 $P_{A,B} > 0.5$	3.5 ± 0.4 $P_{2,3} < 0.001$	NA	2.3 ± 0.3 $P_{A,B} > 0.5$	2.2 ± 0.4 $P_{2,3} < 0.01$	NA
4. After completion of IL-1β administration or spontaneous recovery in group C	4.7 ± 0.3 $P_{A,B} > 0.1$	5.5 ± 0.5 $P_{2,4} < 0.001$ $P_{1,4} > 0.5$	4.5 ± 0.3 $P_{B,C} > 0.05$	3.2 ± 0.2 $P_{A,B} > 0.2$	3.7 ± 0.4 $P_{2,4} < 0.001$ $P_{1,4} > 0.5$	3.0 ± 0.2 $P_{B,C} > 0.1$
5. Duration of leukopenia, days	8 ± 1 $P_{A,B} < 0.01$	5 ± 1	NA	8 ± 1 $P_{A,B} < 0.01$	5 ± 1	NA
6. Restoration interval	8 ± 1 $P_{A,B} > 0.2$	9 ± 1	25 ± 2 $P_{B,C} < 0.01$	8 ± 1 $P_{A,B} > 0.2$	9 ± 1	25 ± 2 $P_{B,C} < 0.001$

NA: not available.

Table 3
Effect of subcutaneous administration of IL-1β on peripheral blood leucocyte count in relation to bone marrow suppression

Parameters studied	Toxic leukopenia		
	II grade (n = 5)	III grade (n = 7)	IV grade (n = 4)
	Leukocytes x 10⁹/L (M ± m)		
1. Leukocyte count before treatment	4.7 ± 0.4	5.6 ± 1.1 $P_{II,III} > 0.2$	8.2 ± 2.5 $P_{III,IV} > 0.2$ $P_{II,IV} > 0.2$
2. Leukopenia before IL-1β administration	2.5 ± 0.1	1.4 ± 0.1	0.7 ± 0.1
3. After administration of IL-1β	5.4 ± 1.0 $P_{2,3} < 0.05$ $P_{1,3} > 0.5$	5.0 ± 0.9 $P_{2,3} < 0.01$ $P_{1,3} > 0.5$ $P_{II,III} > 0.5$	6.5 ± 0.7 $P_{2,3} < 0.001$ $P_{1,3} > 0.5$ $P_{III,IV} > 0.2$ $P_{II,IV} > 0.2$
4. Restoration interval	7 ± 1.5	11 ± 1.5 $P_{II,III} > 0.05$	8 ± 1 $P_{III,IV} > 0.1$ $P_{II,IV} > 0.5$

Table 4
Effect of subcutaneous administration of IL-1β on peripheral blood granulocyte count in relation to bone marrow suppression

Parameters studied	Toxic leukopenia		
	II grade (n = 5)	III grade (n = 7)	IV grade (n = 4)
	Granulocytes x 10^9/L (M ± m)		
1. Granulocyte count before treatment	3.5 ± 0.3	3.9 ± 0.8 $P_{II, III} > 0.5$	7.0 ± 2.2 $P_{III, IV} > 0.05$ $P_{II, IV} > 0.1$
2. Neutropenia before IL-1β administration	1.4 ± 0.1	0.7 ± 0.1	0.2 ± 0.1
3. After administration of IL-1β	3.4 ± 0.7 $P_{2,3} < 0.05$ $P_{1,3} > 0.5$	3.6 ± 0.7 $P_{2,3} < 0.01$ $P_{1,3} > 0.5$ $P_{II, III} > 0.5$	4.3 ± 1.0 $P_{2,3} < 0.01$ $P_{1,3} > 0.2$ $P_{III, IV} > 0.5$ $P_{II, IV} > 0.2$
4. Restoration interval	7 ± 1.5	11 ± 1.5 $P_{II, III} > 0.05$	8 ± 1 $P_{III, IV} > 0.1$ $P_{II, IV} > 0.5$

Table 5
Adverse effects of IL-1β administered by intravenous drop infusion or subcutaneous injection

Adverse effects	Single doses of IL-1β			
	Intravenous drop infusion			Subcutaneous injection
	0.1-1.2 n = 8	1.6-9.0 n = 14	10.0-20.0 n = 78	4.6 n = 16
Hyperthermia	–	6 (42.9%)	53 (67.9%)	10 (62.5%)
I grade	–	2 (14.3%)	21 (26.9%)	7 (43.8%)
II grade	–	4 (28.6%)	28 (35.9%)	3 (18.8%)
III grade	–	–	4 (5.1%)	–
IV grade	–	–	–	–
Chill	–	4 (28.6%)	7 (9.0%)	–
Hyperthermia with chill	–	–	38 (48.7%)	3 (18.8%)
Headache	–	–	13 (16.7%)	–
Giddiness	–	–	2 (2.6%)	–
Weakness	–	–	10 (12.8%)	1 (6.2%)
Nausea	–	1 (7.1%)	–	–
Vomiting	–	–	1 (1.3%)	–
Allergic reactions	–	1 (7.1%)	–	–
Blood pressure decrease	-	-	1 (1.3%)	–
Blood pressure increase	–	1 (7.1%)	–	–
Arthralgia	–	–	2 (2.6%)	–
Hyperemia at the site of injection	–	–	–	5 (31.2%)
Local pain at the site of injection	–	–	–	4 (25.0%)
Without complications	8 (100%)	3 (21.4%)	16 (20.5%)	3 (18.8%)

Authors

M.L. Gershanovich, L.V. Filatova, S.A. Ketlinsky, A.S. Simbirtsev

Institute of Highly Pure Biopreparations, Pudozhskaya St., 7, St. Petersburg, 197110, Russia.

In this issue

Monocyte chemotactic protein-3

Patricia Menten, Anja Wuyts, Jo Van Damme
MCP-3, induction, diseases, structure, receptors.

Adenoviral supply of active transforming growth factor-beta1 (TGF-beta1) did not prevent lethality in transforming growth factor-beta1-knockout embryos

Hedia Chagraoui, Stéphane Giraudier, William Vainchenker, Françoise Wendling
TGF-beta1, cytokine, knockout mice, gene therapy, adenovirus.

Absence of endogeneous interleukin-10 enhances the evolution of murine type-II collagen-induced arthritis

Salvatore Cuzzocrea, Emanuela Mazzon, Laura Dugo, Ivana Serraino, Domenico Britti, Massimo De Maio, Achille P. Caputi
collagen, inflammation, nitric oxide, peroxynitrite, superoxide dismutase, IL-10.

Reduced adrenal response and increased mortality after systemic Klebsiella pneumoniae infection in interleukin-6-deficient mice

Frank H.J. van Enckevort, C.G.J. Sweep, Paul N. Span, Mihai G. Netea, Ad R.M.M. Hermus, Bart Jan Kullberg
corticosterone, cytokine, IL-6-deficient mice, granulocyte recruitment, survival.

Gamma-interferon induces apoptosis of the B lymphoma WEHI-279 cell line through a CD95/CD95L-independent mechanism

K.-E. Ben Jilani, K. Akarid, D. Arnoult, F. Petit, E. Baert, J.-P. Gaillard, J.-C. Ameisen, J. Estaquier
IFN-g, B cells, apoptosis, CD95, caspases, cytokines.

IFN-beta stimulates the production of beta-chemokines in human peripheral blood monocytes. Importance of macrophage differentiation

Laura Fantuzzi, Irene Canini, Filippo Belardelli, Sandra Gessani
MCP-1, MIP-1alpha, MIP-1beta, IFN-beta, monocytes/macrophages, differentiation.

Relationship between cell kinetics and apoptotic effects in TNF-alpha and IFN-gamma-treated human tumour cell lines

Heinz Baisch
apoptosis, c-Myc, cell cycle, cytokines, dual pathways.

L-Buthionine-(S,R)-sulfoximine, an irreversible inhibitor of gamma-glutamylcysteine synthetase, augments LPS-mediated pro-inflammatory cytokine biosynthesis: evidence for the implication of an IkappaB-alpha/NF-kappaB insensitive pathway

John J. Haddad
antioxidant, chemioxyexcitation, cytokines, glutathione disequilibrium, pharmacotherapy, reactive oxygen species, redox/thiol regulation.

Endotoxin regulates the maturation of sterol regulatory element binding protein-1 through the induction of cytokines

Luisa Diomede, Diego Albani, Marco Bianchi, Mario Salmona
SREBP-1, LPS, HepG2, liver, mice.

Regulation of Staphylococcus aureus-mediated activation of interleukin-18 in peripheral blood mononuclear cells

Ulrich Böcker, Tobias Manigold, Joanna M. Watson, Manfred V. Singer, Siegbert Rossol
human, cytokine, bacterial antigen, CD14, signal transduction.

Interleukine-6 (IL-6) synthesis and gp130 expression by human pericardium

Emmanuelle Menet, Pierre Corbi, Cécile Ancey, Franck Morel, Adriana Delwail, Martine Garcia, Anne-Marie Osta, John Wijdenes, Daniel Potreau, Jean-Claude Lecron
IL-6, gp130, pericardium.

Plasmodium falciparum liver-stage antigen-1 peptide-specific interferon-gamma responses are not suppressed during uncomplicated malaria in African children

Adrian J.F. Luty, Martina Bongartz, Philipp Rezbach, Jean-Francois Faucher, Michael R. Hollingdale, Peter G. Kremsner
malaria, cytokine, interferon-gamma, liver.

Immunoexpressions of p21, Rb, mcl-1 and bad gene products in normal, hyperplastic and carcinomatous human prostates

Mar Royuela, María Isabel Arenas, Fermín R. Bethencourt, Manuel Sánchez-Chapado, Benito Fraile, Ricardo Paniagua
p21, Rb, mcl-1, bad, human prostate, benign prostatic hyperplasia, prostatic carcinoma.

Recombinant human interleukin-1 beta: new possibilities for the prophylaxis and correction of toxic myelodepression in patients with malignant tumors I. Phase I-II clinical trials of recombinant human interleukin-1 beta as a leukopoiesis stimulator in cancer patients receiving combination chemotherapy

M.L. Gershanovich, L.V. Filatova, S.A. Ketlinsky, A.S. Simbirtsev
human recombinant interleukin-1 beta, myelopoiesis, myelodepression, cancer chemotherapy.

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

M.L. Gershanovich, L.V. Filatova, S.A. Ketlinsky, A.S. Simbirtsev

human recombinant interleukin-1 beta, leukopoiesis, myelodepression, cancer chemotherapy.

French society of immunology, cytokines

Eric Lelièvre, Isabelle Corre

Les éditions JLE

30 rue Berthollet, Bât. A,
94110 Arcueil, France

+ 33 (0)1 46 73 06 60

contact@jle.com

Publishing Policy

Books and e-books

Want to publish ?

Become a partner



