Interleukin 6 Perfusion Stimulates Reconstitution of the Immune and Hematopoietic Systems after 5-Fluorouracil Treatment

Fumihiko Takatsuki, Akira Okano, Chieko Suzuki, Yuko Miyasaka, Toshibo Hirano, Tadamitsu Kishimoto, Daisuke Ejima, and Yukio Akiyama


ABSTRACT

Effects of interleukin 6 (IL-6) on the functional capacity of the immune and hematopoietic systems in 5-fluorouracil (5-FU)-treated mice were determined. IL-6 (5 x 10^4 units/mouse/day) was administered s.c. for 7 days by implantation of an osmotic pump, since it was demonstrated that a much higher increase in the primary response to sheep RBC was observed by administration of slowly released rather than daily s.c. injection of IL-6. IL-6 perfusion significantly augmented anti-sheep RBC antibody responses depressed by 5-FU (150 mg/kg) treatment. IL-6 also showed a stimulatory effect on hematological recovery and endogenous IL-6 level in serum increased after 5-FU treatment, which suggests that IL-6 may play some role in the recovery of the immune and hematopoietic systems. Finally, we examined the effect of IL-6 on the survival of mice treated with a higher dosage of 5-FU (300 mg/kg). IL-6 perfusion produced a distinct increase in survival rate at Day 30 (74% versus 28%). It is of note that the number of bacteria (identified as Escherichia coli) cultured from the spleen and the liver decreased in IL-6-perfused mice. This IL-6-induced effect was accompanied by enhancement of the immune response. Moreover, the anti-E. coli antibody titer in serum was higher in IL-6-perfused mice than in control mice. These results suggest the possible use of IL-6 for stimulating the reconstitution of the immune and hematopoietic systems after chemotherapy treatment.

INTRODUCTION

Chemically induced cytoreduction is used therapeutically for the treatment of neoplasms. This treatment invariably leads to a decrease in hematopoietic function (1). Many chemotherapeutic agents are also immunosuppressive (2). With decreased hematopoietic and immune function, greater susceptibility to infection has been observed. The therapeutic efficacy of cytoreductive treatment tends to be limited by these toxicities.

Recently, it has been demonstrated that IL-6 is a multifunctional cytokine regulating immune response, acute phase reaction, and hematopoiesis (3). This suggests that IL-6 plays a central regulatory role in host defense mechanisms against infections, inflammation, and tissue injuries. The availability of highly purified recombinant IL-6 confirmed IL-6 activities in vivo as well as in vitro. In vivo administration of recombinant IL-6 has been shown to be effective in augmenting antigen-specific antibody response (4), in inducing acute-phase proteins (5), and in enhancing the circulating number of neutrophils (6, 7). These results prompted us to study further the effect of IL-6 as a cytokine for the decreased hematopoietic and immune function induced by chemotherapy.

A major problem of using IL-6 is that its half-life in vivo is very short (8). Therefore, an important consideration in using IL-6 in vivo is how to achieve constant levels in serum. In order to resolve this problem, a method using mini-osmotic pumps was applied for administration of IL-6. We have already reported that normal mice bearing osmotic minipumps loaded with IL-6 showed a dramatic enhancement in the number of hematopoietic stem cells (CFU-S) and hematopoietic progenitors (CFU-GM) in the spleen (9).

In this paper, we report that IL-6 perfusion is effective in stimulating the recovery of depressed immune and hematopoietic functions in 5-FU-treated mice. Furthermore, we show that IL-6 increases the survival rate in 5-FU-treated mice.

MATERIALS AND METHODS

Mice. Female DBA/2 and C3H/HeJ mice were purchased from Charles River Japan (Kanagawa, Japan) and Nippon Clea Co., Inc. (Tokyo, Japan), respectively. All mice were used at ages of 8 to 12 wk.

Chemicals. Human recombinant IL-6 was prepared by expressing a complementary DNA for IL-6 in Escherichia coli followed by further purification (10). The specific activity of IL-6 was estimated to be 5 x 10^6 units/mg of protein utilizing the Epstein-Barr virus-transformed cell line, SKW6-CL4. IL-6 contained less than 0.3 ng of endotoxin/mg. Heat-treated IL-6 (100°C, 40 min) also was used as a negative control.

Drug Treatments. IL-6 was diluted in PBS (pH 7.4) containing 1% (v/v) syngeneic mouse serum as carrier. IL-6 was administered s.c. once daily or in continuous perfusion by an Alzet mini-osmotic pump (Alzet, Palo Alto, CA; Model 2001) implanted s.c. in control mice, HSA, instead of IL-6, was injected at similar doses. 5-FU (Kyowa Hakko Kogyo Co., Tokyo, Japan) at the dose described in "Results" was injected i.v. into mice 5 h before IL-6 treatment. IL-6 was administered s.c. for 7 days by implantation of an osmotic pump. The concentration of the human IL-6 level in serum was measured by ELISA for IL-6 (11). A combination of rabbit polyclonal anti-IL-6 antibody and mouse monoclonal anti-IL-6 antibody was used.

Assay for Anti-SRBC Antibody Response. Anti-SRBC antibody titers in serum and anti-SRBC PFC in spleen cells were determined after antigen inoculation. Serum anti-SRBC antibody titers were measured by a hemagglutination test as previously described (4). Splenic anti-SRBC direct PFC were counted by the method of Cunningham and Szenberg (12).

Assay for Hematopoietic Progenitor Cell Levels. The spleen and the femur were removed aseptically after blood collection by cardiac puncture. CFU-S was assayed by using the method of Till and McCulloch (13) as described previously (9, 14). CFU-GM was assayed using a conventional methyl-cellulose culture system as described previously (9, 14).

Hematopoietic and Blood Cell Analysis. WBC, RBC, and PLT counts were performed using a Sysmex hematology analyzer (Toa Medical Electronics Co., Ltd., Hyogo, Japan). Spleen cell and bone marrow cell counts were also determined using hemocytometers. Differential counts were performed on smear preparations stained with Wright-Giemsa.
Assay for Mouse IL-6 and IL-3. Hybridoma growth-promoting activity of mouse IL-6 in serum was measured by the proliferation of the IL-6-dependent murine hybridoma, MH60.BSF-2 (11). The IL-6 activity in the sample was expressed as an equivalent amount of human IL-6 required for the same hybridoma growth-promoting activity. Mouse IL-3 activity in serum was also measured by an IL-3-dependent cell line, FDC-P1 (kindly provided by Dr. J. Ihle, Frederick Cancer Research Facility, Frederick, MD) (15).

Quantitation of Bacteria in Organs. The spleen and the liver from 5-FU-treated mice, given either IL-6 or HSA as a control, were removed and homogenized in sterile PBS. Tissue suspensions were plated on standard agar. After overnight incubation at 37°C, the number of CFU was counted. Qualitative assessment of bacterial species was performed by using SYSTEK No. 1 from Eiken Kagaku Co., Ltd. (Tokyo, Japan).

Assay for Chemiluminescence. A previously described chemiluminescence assay (16) was modified and used for assessment of chemiluminescence response of spleen cells from 5-FU-treated mice. Briefly, 0.1 ml of cell suspension (5 x 10⁶/ml) in RPMI medium without phenol red (Grand Island Biological Co., Grand Island, NY) and 0.1 ml of luminol solution (final concentration, 0.2 mmol) (Labosience, Tokyo, Japan) were mixed and preincubated for 2 min at 37°C. Then, 100 μl of 1 μg/ml of PMA (Sigma Chemical Co., St. Louis, MO) were added to start the reaction. The photon emission was measured by using a Model TD-4000 lumiphotometer (Labosience) at 37°C every 0.5 min for 4 min. The area under curves representing photon emission over time was calculated and reported as integrated photon emission.

Measurement of Antibacterial Antibody Response. Antibody titers in sera were determined for pooled serum preparations by a solid phase ELISA. Briefly, bacteria derived from the liver of 5-FU-treated mice were sonicated, dissolved in PBS, and then coated onto immunoplates (Nunc, Denmark) by overnight incubation at 4°C. After saturation of binding sites by bovine serum albumin, plates were washed with PBS, and serum dilutions were added for 1 h at room temperature. After repeated washing with PBS, plates were incubated with alkaline phosphatase-conjugated goat anti-mouse immunoglobulin (Tago, Inc., Burlingame, CA) for 1 h. Alkaline phosphatase activity was measured by using o-nitrophenyl phosphate (Sigma Chemical Co.).

RESULTS

Effect of IL-6 Administered by s.c.-Implanted Mini-Osmotic Pumps on the Primary Antibody Response. We initially examined the relationship between the exogeneous IL-6 level in serum and the augmenting effect of in vivo IL-6 administration on the primary anti-SRBC antibody response. IL-6 was administered s.c. for 7 days either by injections of 5 x 10⁴ units once a day or by implantation of osmotic pumps that released 5 x 10⁴ units per day. When IL-6 was given to mice by single s.c. injection, it rapidly disappeared from the blood, as shown in Fig. 1. However, administration of slowly released IL-6 using mini-osmotic pumps caused a significant prolongation of serum levels of IL-6. A high elvel of serum IL-6 (~2.5 units/ml) was maintained. Next, effects of IL-6 on the primary humoral immune response were compared. DBA/2 mice were given injections i.v. of 1 x 10⁸ SRBC/mouse. On the same day as antigen inoculation, mice received 5 x 10⁶ units/mouse/day of IL-6 by two different administration methods. Eight days after antigen stimulation, mice were bled, and serum anti-SRBC antibody titers were measured. IL-6 perfusion enhanced serum anti-SRBC antibody titer more effectively than IL-6 given by daily single injections for 7 days (Fig. 2). Specifically, continuous perfusion with IL-6 increased the anti-SRBC antibody titer 15.8-fold compared with the conventional daily s.c. administration. In another experiment, it was found that IL-6 perfusion also remarkably enhanced anti-SRBC PFC response compared with control mice perfused with HSA (PFC/spleen x 10⁻³, 154.6 versus 5.7). Furthermore, we found that IL-6 perfusion showed the same biological activity even when C3H/HeJ mice were used, although heat-treated IL-6 did not exhibit any activity (data not shown). IL-6 at this dosage did not induce acute reduction in food intake and body weight in mice.

Effect of IL-6 Perfusion on Recovery of Depressed Humoral Immune Response in 5-FU-treated Mice. The immunorestorative capacities of IL-6 were assessed in vivo in DBA/2 mice immunodepressed by 5-FU treatment (150 mg/kg, i.v.). The number of anti-SRBC PFC in the spleen was measured on Days 3, 5, 7, and 10 after antigen inoculation. As shown in Fig. 3, it was demonstrated that IL-6 perfusion significantly stimulated the PFC response in 5-FU-treated mice. Furthermore, IL-6 restored the depressed anti-SRBC antibody titer in serum almost to the normal level (Table 1).

Effect of IL-6 Perfusion on Recovery of Depressed Hematopoietic Progenitor Cell Levels in 5-FU-treated Mice. We have already shown that normal mice perfused with IL-6 for 7 days showed a marked increase in the number of CFU-S and CFU-GM, although heat-inactivated IL-6 did not exhibit any activity (9). Here, we examined the effect of IL-6 perfusion on hematopoietic progenitors in 5-FU-treated mice. IL-6 or HSA as a control was administered in continuous perfusion 5 h after 5-FU treatment (150 mg/kg). The dose administered was 0.6 to 6.7 x 10⁴ units/mouse/day for 7 days. The numbers of CFU-S and CFU-GM in the spleen were determined 7 days after 5-FU treatment. IL-6 caused a marked dose-dependent increase in CFU-S and CFU-GM. Maximal increases in the numbers of...
Effects of continuous perfusion with IL-6 on SRBC-specific antibody response. DBA/2 mice were immunized with $1 \times 10^6$ SRBC/mouse i.v., and then mice were given injections of IL-6 (5 x $10^4$ units/mouse/day) for 7 days either by a daily conventional s.c. administration or by continuous perfusion using a mini-osmotic pump. Control mice received HSA, instead of IL-6. Mice were bled 8 days after SRBC inoculation. Serum from each mouse was tested for hemagglutination of SRBC. Data are expressed as the mean of five mice per group. The stimulation index is defined as the anti-SRBC titer in treated mice/anti-SRBC titer in control mice ($2^{4.2}$). Two additional experiments showed similar results.

![Graph showing the effects of IL-6 on SRBC-specific antibody response.](image)

Augmentation of SRBC-specific immune response in 5-FU-treated mice by IL-6 perfusion. Four h after 5-FU treatment (150 mg/kg), mice were immunized with $1 \times 10^6$ SRBC i.v. Mice were then perfused with IL-6 (5 x $10^4$ units/mouse/day) or HSA as a control for 7 days. Spleen cells obtained on the indicated days were measured for the number of anti-SRBC direct PFC. Points, mean of triplicate cultures of pooled spleen cells (three mice/group); bars, SD. Anti-SRBC PFC per spleen from normal mice were 2.5, 4.5, and 0.8 x $10^4$ on Days 3, 5, and 7, respectively.

![Graph showing the augmentation of SRBC-specific immune response.](image)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Treatment</th>
<th>Anti-SRBC antibody titer*(log 2)</th>
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<tr>
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<td>IL-6</td>
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</table>

* DBA/2 mice were given injections i.v. of 5-FU (150 mg/kg) 4 h before immunization with SRBC. Mice were immunized i.v. with $1 \times 10^6$ SRBC/mouse (Experiment 1) or $1 \times 10^5$ SRBC/mouse (Experiment 2) and then perfused with IL-6 (5 x $10^4$ units/mouse/day).

Mice were bled 9 days after antigen inoculation. Sera obtained from three mice per group were pooled and measured for anti-SRBC hemagglutination titer. Two additional experiments showed a similar pattern.

CFU-S and CFU-GM were observed in mice perfused with 5 x $10^4$ units of IL-6. Namely, CFU-S and CFU-GM numbers in IL-6-perfused and control mice are as follows: CFU-S/spleen ($\times 10^4$), 21.5 $\pm$ 2.9 versus 5.2 $\pm$ 0.3 ($P < 0.01$); CFU-GM/spleen ($\times 10^4$), 16.7 $\pm$ 1.3 versus 1.8 $\pm$ 0.2 ($P < 0.01$). This optimal dose of IL-6 in stimulating hematopoiesis also augmented the humoral immune response in 5-FU-treated mice, as already described. Kinetic study using the optimal dose of IL-6 (5 x $10^4$ units/mouse/day) indicated that IL-6 perfusion accelerated the recovery of spleen cellularity, CFU-GM, and CFU-S (Fig. 4). On Day 9, the proportion of mature neutrophils in spleen cells increased in IL-6-perfused mice as compared with control mice (17% versus 3%; 28.2 x $10^4$ versus 3.4 x $10^4$/spleen). IL-6 perfusion did not stimulate the recovery of CFU-S in femoral marrow, while IL-6 significantly enhanced CFU-GM in marrow on Days 7 and 9 compared with 5-FU-treated control mice. CFU-GM in femur marrow in IL-6-perfused and control mice were as follows: Day 7, 6.4 $\pm$ 0.7 versus 4.9 $\pm$ 0.1 x $10^4$; Day 9, 25.6 $\pm$ 3.0 versus 9.4 $\pm$ 1.9 x $10^4$. On Day 12, no significant differences in spleen cells, spleen CFU-GM, and CFU-S were observed.

Effect of IL-6 Perfusion on Recovery of Decreased Blood Cell Levels in 5-FU-treated Mice. In contrast with these positive effects on hematopoietic progenitors, no significant difference
in the WBC count in the blood was observed in IL-6-perfused and control mice (Fig. 5). Differential analysis revealed that there was no difference in neutrophil count in IL-6-perfused and control mice (Day 6, 1% versus 1%; Day 12, 25% versus 24%). The RBC counts also were not significantly different in both groups. It is of note that IL-6 significantly stimulated recovery of the PLT count. We also found that this stimulation was accompanied by an enhancement in the number of spleen CFU-megakaryocyte (data not shown).

Elevation of the Serum Level of Endogenous IL-6 after 5-FU Treatment. In order to explore the role of IL-6 in the recovery of hematoimmunological function after 5-FU treatment, we next analyzed the serum level of IL-6 in 5-FU-treated mice. As shown in Fig. 6, a detectable endogenous IL-6 level that was observed within 3 days after 5-FU treatment reached maximum in 6 days. IL-6 became undetectable 12 days after 5-FU treatment. On the other hand, IL-3 was undetectable in the serum at any of the time points examined.

Effect of IL-6 Perfusion on Survival after 5-FU Treatment. To examine the biological importance of the stimulation of the immune and hematopoietic systems induced by IL-6, mice received IL-6 after treatment of a higher dose of 5-FU (300 mg/kg). IL-6 perfusion significantly increased survival as shown in Fig. 7 (74% versus 28% at Day 30; \( P < 0.001 \) by \( \chi^2 \) analysis). We then determined the numbers of bacteria in organs of 5-FU-treated mice in order to assess whether opportunistic infection was responsible for the lethal effect of 5-FU treatment. An apparent decrease in the counts of colonies cultured from the spleen and liver in IL-6-perfused mice was observed compared with control HSA-perfused mice (Table 2). Opportunistic bacteria in the spleen and the liver were identified as \( E. coli \). In addition, spleen cells from IL-6-treated mice showed the enhancement of oxygen radical generation via the stimulation of PMA, as compared with cells from HSA-treated mice. In 5-FU-treated mice, the chemiluminescence response of spleen cells decreased around 10-fold compared with cells from normal mice. Moreover, in a separate experiment, effects of IL-6 perfusion on \( E. coli \)-specific antibody response in 5-FU-treated mice were determined on Day 7 for pooled serum preparations by a solid-phase ELISA. It was found that IL-6 increased the anti-\( E. coli \) antibody (IgG) titer approximately 16-fold compared with control mice, although the level of anti-\( E. coli \) antibody of the IgM isotype did not differ between groups. Next, we determined the total IgG level in serum by using a conventional ELISA assay as described previously (4). There was no difference in the total IgG level in serum in IL-6-perfused and control mice (1.2 ± 0.2 versus 2.3 ± 0.9 mg/ml, \( n = 3 \)). This result is consistent with our previous report (4) that no augmentation of polyclonal antibody production by IL-6 administration was observed.

**DISCUSSION**

In the present study, we have demonstrated the ability of IL-6 to stimulate recovery of immune and hematopoietic systems after 5-FU treatment. The complete abrogation of IL-6 activity by heat treatment confirmed IL-6 as the agent which augments immunohematological functions. We have also shown the ability of IL-6 to prolong survival in 5-FU-treated mice, which correlates with a decrease in bacterial infection in organs.
The ability of IL-6 to enhance the primary humoral immune response was dependent on its method of administration. Slowly released IL-6 using a mini-osmotic pump succeeded in maintaining a constant serum level of IL-6, and this administration was more effective than a daily s.c. injection of IL-6 in inducing antigen-specific antibody in the serum. Furthermore, it was found that the serum IL-6 level increased after 5-FU treatment. Exogenously administered IL-6 may cooperate with endogenous IL-6 to stimulate recovery of hematopoietic function in 5-FU-treated mice.

Recent in vitro studies have shown that IL-6 plays an important role in hematopoiesis, especially in early hematopoiesis (14, 17, 18). IL-6 has the capacity to support IL-3-dependent growth of multipotential hematopoietic progenitors. IL-6 administration also enhances production of hematopoietic stem cells (CFU-S) (9). In this study, we observed that IL-6 facilitates host recovery from hematological suppression induced by 5-FU treatment. Koike et al. (18) suggested that some factors other than IL-3 in fetal bovine serum also act with IL-6 synergistically in colony formation from spleen cells of 5-FU-treated mice. IL-6 may act synergistically with endogenous unidentified serum factors or other colony-stimulating factors in the recovery of the hematological system after 5-FU treatment. The effect of IL-6 on stimulation of recovery of depressed production of CFU-S and CFU-GM induced by 5-FU treatment was more apparent in the spleen than in bone marrow. IL-3 or granulocyte colony-stimulating factor also induced a similar activity (19–21). The reason for this activity remains unclear; however, CFU activity may move from bone marrow into peripheral blood and then to the spleen and other organs.

We demonstrated here that IL-6 perfusion is able to increase survival in 5-FU-treated mice. The mechanism of this IL-6 effect is unclear. Further studies are needed to elucidate what mechanism(s) is responsible for IL-6-induced prolongation of survival in 5-FU-treated mice. IL-6 may induce protection against death from an opportunistic infection by enhancement of cellular and/or humoral defense mechanisms in 5-FU-treated mice, since the number of E. coli cultured from the spleen and the liver was apparently fewer in IL-6-perfused mice than in control mice. IL-6 stimulated recovery of the production of CFU-S and CFU-GM and also of spleen cellularity, although IL-6 did not influence WBC or neutrophil counts in the blood. Fifty % of the increased number of spleen cells was found to be due to enhancement of the mature neutrophil number. Accordingly, with respect to cellular defenses, stimulation of granulopoiesis in organs is considered a major mechanism. In fact, the oxidative burst response of spleen cells was higher in IL-6-perfused, 5-FU-treated mice than in control mice. In our system, the liver also may play a role in local tissue defense, since it is known that hematopoiesis in adult mice can return to the liver in conditions of stress or damage to the bone marrow or spleen (19). Histological analysis will be required for evaluating this point. With respect to humoral defense, increased anti-E. coli IgG antibody titer by IL-6 administration may have an important role in the protection of E. coli. A possible explanation for the beneficial influence of IL-6 in gram-negative infection could be through the interaction of local tissue phagocytic cells and bacteria-specific antibody as an opsonin. IL-6 also is known to be an inducer of acute phase proteins in vivo (5). Acute phase proteins, such as an endotoxin-binding protein, may also be responsible for the protective effect of IL-6. Furthermore, IL-6 administration may have an effect on the regeneration of intestinal mucosal cells.

It is of note that IL-6 perfusion stimulated the recovery of PLT counts in blood after 5-FU treatment. This result is supported by work which shows that IL-6 is a potent direct-acting growth factor for murine megakaryocytes with activity-promoting maturation of that lineage (22). In addition, it has been found that in normal mice IL-6 in vivo acts on maturation stages in megakaryocytopoiesis and promotes PLT production (23). Our findings that IL-6 administration increases the immune

Table 2 Effect of IL-6 perfusion on number of bacteria and chemiluminescence response in organs from 5-FU-treated mice

<table>
<thead>
<tr>
<th>Mice*</th>
<th>No. of bacteria/organ</th>
<th>Chemiluminescencea (integrated photon emission)</th>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>5</td>
<td>86</td>
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</table>

a Five h after 5-FU treatment, five DBA/2 mice per group were perfused with IL-6 (5 × 10^6 units/mouse/day) or HSA as a control for 7 days.

b Spleen and liver were removed 9 days after 5-FU treatment. Tissue suspensions were plated on agar, and the number of CFU was counted after overnight incubation.

c Spleen cells (5 × 10^6) were activated with PMA at a final concentration of 330 ng/ml.

EFFECT OF IL-6 ON 5-FU-TREATED MICE

![Fig. 7. Effect of IL-6 perfusion on the survival of 5-FU-treated mice. Five h after 5-FU treatment (300 mg/kg), mice were perfused with IL-6 (5 × 10^6 units/mouse/day) for 7 days (n = 28). Control mice received HSA injections (n = 23). Mice were followed for up to 30 days with no further deaths observed. The survival rate was significantly different in both groups (P < 0.001 by x^2 analysis).](image-url)
and hematological functions and survival in 5-FU-treated mice suggest the possible use of IL-6 in combination with chemotherapeutic agents in the treatment of human cancer. This ability of IL-6 may allow clinicians to increase the frequency or dosage of chemotherapeutic agents.

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REFERENCES

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