Effects of Recombinant Interleukin-2 Administration on Cytotoxic Function Following High-Dose Chemo-Radiotherapy for Hematological Malignancy

Abstract

Although the frequency of remission induction in acute leukemia has increased steadily over the past two decades, the overall survival in adults treated with cytotoxic chemotherapy alone remains poor: these effects are seen after both autologous and allogeneic transplantation but which may contribute to the reduced relapse risk observed after these procedures. Interleukin-2 (IL-2) in vitro augments this reduction in leukemic relapse, which is augmented in vivo. We studied changes in number, phenotype, and function of the CD3+ T cells and CD16+ natural killer (NK) cells in patients with acute myeloid leukemia and multiple myeloma receiving IL-2 infusions. Patients with acute myeloid leukemia and multiple myeloma were treated because malignant cells from patients who have undergone autologous and allogeneic bone marrow transplant (BMT) and may contribute to the reduced relapse risk alone: these effects are seen after both autologous and allogeneic BMT. A contribution to the reduced relapse risk after BMT may be made by the endogenous generation of activated killer (AK) lymphocytes, which circulate following BMT and may result in improved relapse-free survival following chemotherapy or BMT. IL-2 infusions during the phase of marrow regeneration following chemotherapy or BMT patients studied had all received autologous marrow. Median age was 38 years (range, 18 to 67 years). Nine patients were men, and seven after combination cytotoxic chemotherapy. IL-2 was given soon after treatment, when recovering neutrophil count exceeded 0.5 x 10⁹/L, in an effort to generate rebound lymphocytosis after the termination of treatment. IL-2 was given soon after treatment, when recovering neutrophil count exceeded 0.5 x 10⁹/L, in an effort to generate rebound lymphocytosis after the termination of treatment.

MATERIALS AND METHODS

Details are shown in Table 1. Patients were treated with IL-2 infusions. Twelve patients with acute myeloid leukemia (AML) and four with multiple myeloma (MM) are included.

Intracellular Lysozyme

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Table 1. Clinical Details

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Treatment</th>
<th>Dose IL-2 (µg/m²/d)</th>
<th>Total Dose IL-2 (µg/m²)</th>
<th>Total Dose IL-2 (x 10⁶ U/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-chemotherapy</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>67/M</td>
<td>AML M4</td>
<td>MACE</td>
<td>Escalating</td>
<td>1,800</td>
<td>5.8</td>
</tr>
<tr>
<td>2</td>
<td>20/M</td>
<td>AML M3</td>
<td>Ara-C</td>
<td>160, 320</td>
<td>480, 960</td>
<td>1.5, 3.0</td>
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<tr>
<td>3</td>
<td>33/M</td>
<td>AML M4</td>
<td>Ara-C</td>
<td>176, 350</td>
<td>525, 1,050</td>
<td>1.6, 3.3</td>
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<tr>
<td>4</td>
<td>45/M</td>
<td>AML M3</td>
<td>Ara-C/mitozantrone</td>
<td>315, 475, 580</td>
<td>945, 1,740, 2,375</td>
<td>3.0, 7.5, 5.5</td>
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<td>5</td>
<td>30/M</td>
<td>AML M4</td>
<td>Ara-C/mitozantrone</td>
<td>600</td>
<td>2,500</td>
<td>6.0</td>
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<td>6</td>
<td>18/M</td>
<td>AML M2</td>
<td>MACE</td>
<td>630, 630</td>
<td>3,150, 3,150</td>
<td>7.5, 7.5</td>
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<tr>
<td>7</td>
<td>33/F</td>
<td>AML M2</td>
<td>Ara-C/mitozantrone</td>
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<td>1,875</td>
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<td>Post-autograft</td>
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<td>8</td>
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<td>ABMT</td>
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<td>2,700</td>
<td>8.6</td>
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<tr>
<td>9</td>
<td>58/M</td>
<td>MM</td>
<td>ABMT</td>
<td>160, 315</td>
<td>480, 1,575</td>
<td>1.5, 5.0</td>
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<td>10</td>
<td>29/F</td>
<td>AML M6</td>
<td>ABMT</td>
<td>195, 390</td>
<td>585, 600</td>
<td>1.8, 1.9</td>
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<td>11</td>
<td>58/F</td>
<td>AML M7</td>
<td>ABMT</td>
<td>525, 450</td>
<td>2,500, 1,800</td>
<td>4.3, 31</td>
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<td>12</td>
<td>55/F</td>
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<td>ABMT</td>
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<td>3,000, 3,000</td>
<td>5.0, 5.0</td>
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<td>13</td>
<td>22/F</td>
<td>AML M6</td>
<td>Ab MT</td>
<td>700</td>
<td>3,500</td>
<td>7.0</td>
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<td>14</td>
<td>56/F</td>
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<td>ABMT</td>
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<td>1,600, 1,750</td>
<td>2.7, 3.3</td>
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<tr>
<td>15</td>
<td>38/M</td>
<td>MM</td>
<td>ABMT</td>
<td>375</td>
<td>1,875</td>
<td>3.6</td>
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Abbreviations: MM, multiple myeloma; MACE, m-amsacrine (100 mg/m² IV x 5), cytosine arabinoside 100 mg/m² x 5, etoposide 100 mg/m²/d xIV x 5); Ara-C, cytosine arabinoside (0.5 to 1.0 g/m² twice daily IV x 5); Ara-C/mitozantrone, cytosine arabinoside (0.5 to 1.0 g/m² twice daily IV x 5) and mitozantrone (10 mg/m² IV x 5).

Eligibility criteria included: (1) myeloablative chemotherapy with or without total body irradiation 2 to 5 weeks before IL-2 therapy, (2) age between 16 and 70 years, (3) normal renal and hepatic function, (4) absence of active infection, and (5) no prior treatment with biologic response modifiers. Patients received intravenous (IV) infusions of IL-2 over either 6 or 24 hours for periods of 3 to 5 days. Doses of IL-2 were escalated within courses for two patients and between courses of therapy in the remainder. Dosage of IL-2 administered varied from 160 to 700 µg/m²/d. Three to 5-day infusions of IL-2 were well tolerated by patients without requirement for intensive care unit support. Full clinical details of IL-2 administration and adverse events are documented elsewhere.7 Where possible, patients were investigated immediately before treatment, every 48 hours during infusion, and again 48 to 72 hours after the completion of therapy.

Recombinant IL-2. Recombinant IL-2 (rIL-2) cloned in Escherichia coli, with a specific activity between 1.7 and 3.2 x 10⁸ U/mg protein as measured by tritiated thymidine uptake of CTLL-2 cells, was provided by Glaxo IMB (Geneva). The activity of each unit is equivalent to 1.0 U of the reference material of the Biological Response Modifiers Program (BRMPs). Lymphopohilized material was reconstituted in 46 ml sterile water for injection and human albumin at a 5% concentration added as a protein carrier.

Determination of hematologic parameters. Complete blood counts were performed using an automated cell counter (Ortho ELT 800 WS, Ortho Diagnostic Systems, Boston, MA) and differential counts verified by examining May-Grünewald-Giemsa stained blood films by light microscopy.

Preparation of mononuclear cells. Venous blood (60 to 100 mL) was centrifuged on Ficoll (Nycomed, Norway) and washed in RPMI 1640 medium with 10% heat-inactivated fetal calf serum (FCS) and penicillin/streptomycin (100 U/mL).

Immunophenotyping. Immunophenotyping was performed using a two-color indirect immunofluorescent technique in a microtiter plate system. One to 2 x 10⁶ cells were washed in phosphate-buffered saline (PBS) with 0.2% azide before staining with: OKT3 (CD3, pan T cell), Leu 3a (CD4, helper T cell), RFT8 (CD8, cytotoxic/suppressor T cell), Leu 11b (CD16, NK cell), Leu 7 (CD57, NK cell), Leu 19 (CD56, NK cell), and Tac (CD25, IL2 receptor). After incubation and washing, cells were stained with fluorescein or rhodamine conjugated goat anti-mouse IgG or IgM (Southern Biotechnology, Birmingham, AL), incubated, washed, and examined using a fluorescent microscope. RFT8 was a gift of Professor G. Janossy (Department of Immunology, Royal Free Hospital), reagents of the Leu series were obtained from Becton Dickinson (Cowley, England), and OKT3 from Ortho (High Wycombe, England).

Cellular cytotoxicity (NK, LAK activity). Cytotoxicity of peripheral blood mononuclear cells (PBMCs) was assessed using a standard 4-hour Cr³⁺ release assay. PBMCs were resuspended in RPMI 1640 medium with 10% heat-inactivated fetal calf serum at a concentration of 5 x 10⁶/mL. Target cells were labeled with NaCr³⁺ and resuspended in RPMI/10% FCS at a concentration of 5 x 10⁶/mL. In V shaped microtiter wells triplicate dilutions of effector cells were made to give four effector to target ratios. Equal volumes of target cells were added to all wells. Values for maximum and spontaneous release were obtained by substituting Triton-X and RPMI 1640/10% FCS, respectively, for effector cell suspension. After 4 hours' incubation at 37°C, plates were spun and 100 µL of supernatant fluid was aspirated for isotope counting. Percent specific cytotoxicity was calculated from the following formula:

\[
\text{Experimental Release} - \text{Spontaneous Release} \\
\times 100
\]

Assessment of LAK precursors in peripheral blood. LAK precursor (LAKp) activity was assessed by the ability of PBMCs to lyse IL-2 targets after short in vitro incubation with IL-2. PBMCs were resuspended in RPMI 1640 medium with 10% FCS at a concentration of 2 x 10⁴/mL and incubated with rIL2 at a concentration of 500 U/mL at 37°C for 2 hours. Cells were washed in RPMI and resuspended in RPMI/10% FCS at a final concentration of 5 x 10⁴/mL before use in cytotoxicity assays.

Maintenance of cell lines. Cell line K562, (NK-sensitive target) was maintained in continuous culture in RPMI 1640 medium.
EFFECTS OF IL-2 ON CYTOTOXIC FUNCTION

LAK activity was tested supplemented with glutamine, penicillin, streptomycin, and 10% vol/vol heat inactivated fetal calf serum. LAK activity was tested using an NK-resistant LAK-sensitive Epstein-Barr virus transformed B-lymphoblastoid cell line (B-LCL), established from the peripheral blood of a BMT donor and maintained in continuous liquid culture.

Depletion of peripheral blood lymphocytes. PBMCs were incubated for 15 minutes at room temperature with OKT3 (CD3) and RFT8 (CD8) and Leu 11b (CD16) or Leu 7 (CD57, NK cell) added at saturating concentration. A 1/3 dilution of baby rabbit C′ was added and the cells incubated at 37°C for 40 minutes. A second round of C′-mediated lysis was performed after washing. Control cultures were treated with C′ alone. Immunophenotyping after depletion showed less than 5% positive residual cells in all cases.

Inhibition of clonogenic progenitor growth. Cryopreserved leukemic blast cells were thawed, washed once in RPMI 1640 medium, resuspended in McCoy's medium supplemented as previously described, and incubated overnight at 37°C in 5% CO2. Blasts were incubated alone or with PBMCs from patients receiving or about to receive IL-2, at a ratio of 1:3. Viability was assessed after overnight incubation and blasts at a final concentration of 10^5/mL were plated in 0.3% agar in 35-mm Petri dishes. Triplicate cultures were performed. Recombinant human GM-CSF 1,000 pmol/L and IL-3 56 U/mL (Glaxo ImmunoGenetics, Geneva) were used as a source of colony stimulating activity. Clusters, between 3 and 40 cells and colonies over 40 cells, were counted on day 14, using histochemical identification of leukemic cells.

RESULTS

Effect on lymphocyte number and phenotype. To analyze the effect of IL-2 on regenerating lymphocytes, cell numbers and phenotype were determined pre, during, and post-IL-2 infusions. Infusions were associated with a significant early lymphopenia affecting all subsets and occurring within 24 hours. Lymphocyte numbers fell from a pretreatment mean of 2.0 ± 0.3 x 10^9/L to 0.8 ± 0.1 x 10^9/L (P < .001) (Fig 1) but recovered as infusion continued. Rebound lymphocytosis occurred after IL-2 treatment, peaking 48 to 72 hours after infusion was terminated, at a mean level of 8.0 ± 2.8 x 10^9/L (P < .03 compared with pretreatment value). The same pattern of initial fall, gradual recovery with continuing infusion, and rebound lymphocytosis following infusion affected all phenotypic subpopulations studied (Table 2) with the exception of cells expressing the CD25 antigen (p55 IL-2 receptor). The overall number of these cells remained constant even during the early part of infusion despite the initial lymphopenia, because of a rapid increase in the percentage of CD25+ cells. By day 4 to 5 of infusion, the total number of CD25 positive cells in the circulation increased almost sevenfold compared with pre-infusion levels. The absolute numbers of CD16+ and CD8+ cells also increased significantly (Table 2). There was a small but statistically not significant rise in the CD4 positive subsets.

Although both the absolute numbers and the relative proportion of circulating cells expressing the CD16 (NK cell) antigen increased significantly during infusion (Fig 2), further phenotypic analysis of NK subpopulations showed no significant alteration in CD3− Leu 19+ or CD3+ Leu 19+ subpopulations. Pre-infusion CD3− Leu 19+ represented 12.3% ± 3.2% of circulating cells, and 16.6% ± 4.5% at day 4 of infusion. CD3+ Leu 19+ cells formed less than 2% of cells both pre-infusion and by day 4.

Effect on cytotoxic effector function. Effector function was measured pre-IL-2, 3 to 5 days after starting treatment, and 48 hours after the infusion was terminated.

NK activity. IL-2 infusion markedly increased NK activity (Fig 3). Mean Cr′ release from the NK target K562 increased from 18.4% ± 2.3% pre-IL-2 to 42.1% ± 3.6% during treatment (n = 21, E:T ratio 50:1, P < .001) (Fig 4). This effect persisted during the period of infusion but declined within 48 hours of its termination.

Table 2. PBMC Positive for CD4, CD8, CD16, and CD25 Antigens at Different Times During IL-2 Infusion

<table>
<thead>
<tr>
<th></th>
<th>Pre-infusion</th>
<th>Day 1-3</th>
<th>Day 4-5</th>
<th>Post-infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 20)</td>
<td>(n = 14)</td>
<td>(n = 13)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>PBMC</td>
<td>2.1 ± 0.4</td>
<td>0.8 ± 0.1</td>
<td>3.6 ± 0.9</td>
<td>6.6 ± 3.0</td>
</tr>
<tr>
<td>CD4 (helper/inducer)</td>
<td>0.57 ± 0.08</td>
<td>0.12 ± 0.03</td>
<td>0.87 ± 0.16</td>
<td>2.19 ± 0.28</td>
</tr>
<tr>
<td>CD8 (cytotoxic/suppressor)</td>
<td>0.86 ± 0.07</td>
<td>0.20 ± 0.04*</td>
<td>1.19 ± 0.19*</td>
<td>1.87 ± 0.31*</td>
</tr>
<tr>
<td>CD16 (NK cell)</td>
<td>0.22 ± 0.03*</td>
<td>0.08 ± 0.03*</td>
<td>0.75 ± 0.14*</td>
<td>1.04 ± 0.17*</td>
</tr>
<tr>
<td>CD25 (Tac, IL2R)</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.02</td>
<td>0.53 ± 0.13*</td>
<td>0.85 ± 0.13*</td>
</tr>
</tbody>
</table>

Samples were analyzed immediately before infusion, between days 1 and 3 or days 4 and 5 of infusion, and 24 to 72 hours after infusion was terminated. Figures give cell count x 10^9/L (mean ± SEM).

*Significantly different from pre-infusion value, P < .005.
LAK activity. Circulating lymphocytes with the ability to kill NK-resistant but LAK-sensitive targets appeared in the circulation or increased in activity during 16 of 19 IL-2 infusions studied (Fig 3). Mean Cr^51 release from the B-LCL LAK targets increased from 5.9% ± 1.9% to 15.5% ± 3.1% during treatment (n = 19, E:T ratio 50:1, P < .001) (Fig 4). LAK cells disappeared from the circulation within 48 to 72 hours of stopping infusion.

Phenotype of IL-2-induced LAK effectors. Phenotypically the majority of LAK cells are either CD3+ (CD8+/−) CD16− (T cell derived) or CD3− CD16+ (NK cell derived). To determine whether both subpopulations were represented in the IL-2-treated patients we used complement mediated lysis with monoclonal antibodies to CD3 and CD8 antigens ("T LAK") or to CD16 and Leu 7 ("NK LAK"). In all patients studied, fewer than 2% of Leu 7+ or CD16+ cells were CD3+. Depletion of either subset alone did not abolish LAK activity indicating that effector function was present in both CD3+ CD16− and CD3− CD16+ subpopulations. However, depletion of both NK and T LAK cells by a combination of CD8, CD3, CD16, and Leu 7 monoclonal antibody + C' almost completely abrogated cytotoxicity against LAK targets (Fig 5).

Generation of cells with cytotoxic effector function. To determine whether IL-2 infusions in vivo after chemotherapy/BMT produce maximal activation of cytotoxic effector function, we treated PBMCs with IL-2 in vitro before use in NK and LAK assays. PBMCs taken from patients before and during IL-2 infusion, and stimulated briefly with exogenous IL-2, showed a striking increase in cytotoxicity against LAK targets during IL-2 infusion. Cytotoxicity increased
from a mean of 14.1% ± 2.4% before treatment to 38.6% ± 4.2% during infusion (n = 18, E:T ratio 50:1, P < .001). Activity against the NK-sensitive K562 line increased from 48.3% ± 4.3% to 63.0% ± 4.5% (n = 18, E:T ratio 50:1, P = .002).

Inhibition of myeloid blast cluster and colony growth. PBMCs taken from patients immediately before IL-2 infusion produced less than 10% inhibition of blast cluster and colony growth. PBMCs taken from patients during IL-2 infusion and pre-incubated with myeloid blasts reduced cluster growth from a mean of 204.2 ± 46.5 to 67.6 ± 18 clusters (n = 8, P = .001) and colonies from 47.0 ± 11.6 to 8.7 ± 3.0 colonies (n = 8, P = .005) representing a 46.5% and 70.1% inhibition in cluster and colony growth, respectively.

**DISCUSSION**

Treatment of acute leukemia with either autologous or allogeneic BMT produces a lower risk of subsequent relapse than treatment with chemotherapy alone. Although this reduction in risk is in part a consequence of the increased chemotherapy and total body irradiation used before BMT, there is increasing evidence that the lower relapse rate is also dependent on a number of effector mechanisms derived from the regenerating marrow. These effector mechanisms together comprise a graft versus leukemia (GVL) effect. Following allogeneic BMT, the major effectors are thought to be MHC restricted alloreactive T cells. However, the observation that autologous marrow transplantation is also associated with a reduced relapse risk implies that other effector mechanisms exist, since MHC-restricted alloreactive T cell killing will not be present in these patients. One potential mechanism that has been identified following both allogeneic and autologous BMT is mediated by cytokine secreting MHC unrestricted AK cells, which appear spontaneously post-BMT and circulate in the peripheral blood. These endogenous AK cells may help to eradicate residual malignant cells either through direct cytotoxicity or via the release of cytokotoxic cytokines. Because of their potential importance in disease eradication we have investigated whether infusion of IL-2 can augment AK function after ABMT and induce it after chemotherapy alone.

One possible hindrance to attempts to boost cytotoxicity with IL-2 after chemotherapy/ABMT is that the target cells for the cytokine have regenerated from progenitors that may have a limited capacity to respond appropriately to IL-2 stimulation due to damage by recent exposure to high dose chemotherapy. Ex vivo studies have shown that cells taken from such patients retain the potential to respond to incubation with rIL-2; the present investigation shows that the same enhanced cytotoxicity can be achieved in vivo. Lymphocytes regenerating following exposure to intensive chemotherapy therefore retain the capacity to respond to achievable blood levels of infused IL-2 with the generation of AK cells. Lymphocytes from these patients also undergo the same IL-2-dependent redistribution previously observed in individuals with solid tumors receiving treatment with IL-2 alone. Profound lymphopenia occurred on initial infusion of IL-2 followed by rebound lymphocytosis on cessation of therapy. Initial reduction in lymphocyte number probably represents a general increase in lymphocyte adhesion to vascular endothelium and subsequent migration to extravascular spaces. The later increase in PBL numbers with more prolonged exposure to IL-2 also involved all subpopulations, although significant increases in the percentage of positive cells occurred in CD16 positive and IL-2 receptor positive subsets. This may be a consequence of intravascular lymphocyte proliferation, extravascular proliferation, redistribution of sequestered cells, or a combination of all three phenomena.

There was also an increase in the percentage of PBMCs expressing the NK associated Leu-19 (CD57) Ag during IL-2 infusion although this did not reach statistical significance. Increases in the percentage of Leu-19 positivity described in other reports have been dependent on the duration of infusion and even after 7 days of IL-2 administration they have been modest. As the majority of courses of IL-2 in our patients were of 3 to 5 days’ duration only, these relatively small increments are not unexpected. It seems likely that analysis of a larger patient base will reveal that IL-2 induces a significant increase in Leu-19+ cells as well as in CD16+ lymphocytes.

NK and LAK cytotoxic effector function of the circulating lymphoid cells were both significantly increased. NK activity increased in 18 of 21 courses studied while cells with the capacity to kill LAK-sensitive targets appeared in the circulation during 16 of 19 courses. These circulating activated lymphoid cells also mediate antileukemic effector function as demonstrated by the effect of the lymphocytes on clonogenic blast growth in agar. Finally, treatment with IL-2 produced a marked increase in the number of circulating...
activation" induced by mediate LAK cytotoxicity, a state of "pre-
the potential to may represent a genuine recruitment of progenitor cells with
manipulation when IL-2 exposure decayed during laboratory
lymphoid cells regenerating after chemotherapy/BMT
tion between these possibilities, we can be confident that
is removed.
Although our data do not permit the differentia-
1977
J Cancer 36:770,
1979
AJ,
nonlymphocytic leukemia: Use of anthracycline-cytosine arabino-
mens. Blood
2340
of this subset alone does not abolish LAK function.
show contain lymphocytes
depletion
depletion
of NK-LAK is required to completely
Additional depletion
to have distinctive patterns of tissue distribution and
CD3-
target cell specificities38'39; both may
also have different target cell specificities38'39; both may
depletion
neutralizing cell surface IL-2 receptors
the generation of anti-IL-2 antibodies during
synergistic actions of cytokines into the serum or the release of down-regulatory
target cell specificities38'39; both may
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12'3
Preisler HD, Rustum Y, Henderson EF, Bjornsson 5, Craven
3.
Leithner Anzick, Rees JKH, Sandler RM, Challener J, Hayhoe FGJ: Treatment
2.
Gray RG, Swirsky D, Hayhoe FGJ: Principal
4. Preisler H, Davis RB, Kirshner J, Dupre E, Richards F,


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33. Mookerjee BK, Chen PB, Pauly JF: IL-2 induced polyclonal proliferation of human peripheral blood lymphocytes: Functional and phenotypic characteristics of proliferating cells. Immunology 66:176, 1989


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