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ACHIEVEMENT AND MAINTENANCE OF COMPLETE REMISSION IN A PATIENT WITH ACUTE MYELOGENOUS LEUKEMIA AFTER WEEKLY ADMINISTRATION OF INTERLEUKIN-2

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ABSTRACT

Several groups have used high doses of interleukin-2 (IL-2), achieving a significant rate of responses in patients with acute myelogenous leukemia (AML). These results have mainly been observed in AML patients with limited disease (bone marrow blasts <25%), but this therapy is associated with significant toxicity which is dose-related. In this report we describe a patient with AML in whom conventional chemotherapy had achieved partial remission. This patient received subcutaneously intermediate doses of IL-2 (12×10^6/m^2/week) and achieved complete remission which was maintained for eleven months. The side effects of IL-2 were mild. The results of this report document the antileukemic effect of IL-2 in AML with limited disease as well as the efficacy of subcutaneous maintenance treatment for prolonged periods.

Key words: acute myelogenous leukemia, interleukin-2

Interleukin-2 (IL-2) is a 15-kd glycoprotein secreted by antigen-activated T cells which has a variety of *in vivo* immunomodulatory effects.[1] The production of IL-2 using recombinant DNA technology has allowed extensive testing of IL-2 in humans. Several studies have documented the ability of IL-2 administration in high doses to induce signifignant tumour responses in patients with refractory malignant lymphoma and acute myelogenous leukemia (AML).[2-6] This therapy, however, is associated with significant toxicity which is dose-related. Therefore, there is a trend towards using low doses of IL-2 only after intensive chemotherapy or autologous bone marrow transplantation, aiming at the eradication of minimal residual disease.[2,6-9] In this report we describe the achievement and maintenance of complete remission after weekly administration of intermediate doses of IL-2 in a patient with AML in whom conventional chemotherapy had achieved partial remission.

Case report

A 62-year-old man with chronic obstructive lung disease was affected by *de novo* AML. The diagnosis of AML, FAB subtype M1, was established by cytochemistry and immunocytochemistry (APAAP method). At the onset of the disease the main symptoms and signs were fatigue, fever above 39°C, right pneumonia with pleurisy and severe anemia (Ht:16%). Because of his condition, the patient received low doses of conventional chemotherapy consisting of cytosine arabinoside (ara-C) 100 mg/m^2 by constant infusion days 1-5, mitoxanthrone 10 mg/m^2 days 1 and 3, and etoposide 100 mg/m^2 day 1 and a partial remission was achieved (marrow blasts: 9%). One month later, an increase in marrow blasts to 17% as well as the presence of blasts in the peripheral blood indicated a progression of the disease. At this time, the administration of intermediate doses of IL-2 was decided because of the patient's severe chronic lung disease.

The patient received recombinant IL-2 (Pro-

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leukin), that was administered subcutaneously using a weekly dose of 12×10^6 IU/m^2, divided into two daily doses, continuing until relapse. The first two doses of IL-2 were administered in the hospital, followed by self-injections in an outpatient setting. During the IL-2 administration, the patient received prophylactic therapy of pentoxyphylline (PTX) 400 mg×2 and ciprofloxacin 500 mg×2, 24 hours before and after the IL-2 administration. The side effects of IL-2 were mild and consisted of transient fever up to 38.5°C, general malaise, occasional nausea and local erythema at the site of the injection.

Complete remission (CR) was achieved one month after starting IL-2 therapy, while at the same time an absolute lymphocytosis with large granular lymphocytes and eosinophilia were observed in the peripheral blood and bone marrow. From the immunophenotypic analysis an increased proportion and absolute number of CD2$^+$, CD3$^+$ and CD16$^+$ lymphocytes were observed, as well as an increased expression of activation markers CD25 and HLA-DR. The CD4-to-CD8 ratio increased five months after the initiation of IL-2 therapy. These findings, which were in agreement with the literature,[1,9] remained until relapse of the disease.

Eleven months after the initiation of IL-2 therapy a proportion of marrow blasts was established of more than 10%, while one month later, the proportion of marrow blasts increased to 26%. The leukemic relapse showed the same cyto-immunological characteristics of the initial diagnosis, while a significant decrease in the proportion of CD3$^+$, CD4$^+$, CD16$^+$ and CD25$^+$ lymphocytes was observed in the peripheral blood.

The patient received conventional chemotherapy consisting of ara-C 200 mg/m^2 by constant infusion days 1-5, mitoxanthrone 10 mg/m^2 days 1-3, and etoposide 100 mg/m^2 days 1-3 and a second partial remission was achieved (marrow blasts: 7%).

Subsequently, neither consolidation chemotherapy nor IL-2 was applied and the administration of low doses of ara-C was decided because of the patient's severe chronic lung disease. Four months later, the condition of the patient remains stable.

Discussion

Several groups have used IL-2 therapy in high doses achieving a significant rate of responses in patients with AML. In these patients, IL-2 therapy has induced complete remissions, which in some cases have exceeded the length of the previous longest remission.[2,4-6,9] However, this therapy is associated with significant dose-related toxicity. CRs due to IL-2 therapy have mainly been observed in patients with limited disease (marrow blasts <25%).[4,5,9] In our report CR was achieved in a patient with residual bone marrow blastosis (marrow blasts: 17%) by administration of intermediate doses of IL-2 which therefore led to mild toxicity only. This finding suggests that IL-2, even at low doses, may exert an significant degree of activity.

Secondary cytokines, including interferon-γ and tumor necrosis factor-α (TNF-α), are known to be released *in vivo* after IL-2 administration.[1-3] These cytokines exert antitumour activity but are responsible, especially TNF-α, for the significant toxicity of IL-2. PTX is a methylated xanthine that inhibits the production of TNF-α and ciprofloxacin is a quinolone that modifies the metabolism of methylxanthines, increasing their levels in the blood. Preliminary trials indicate that PTX and ciprofloxacin administered with IL-2 therapy was associated with significantly less toxicity, while objective tumor responses were observed simultaneously.[10] Our patient had been receiving IL-2 for eleven months, when a leukemic relapse was observed. This occurrence discouraged us to re-administer IL-2 to the patient after the second partial remission.

In conclusion, the results of this report indicate that IL-2 therapy may achieve complete and prolonged remissions in AML patients with limited disease even with intermediate doses. Furthermore, these results indicate the efficacy of subcutaneous maintenance treatment with intermediate doses of IL-2 on an outpatient basis for prolonged periods. However, it will be necessary to define the role of immunity in cancer patients progressing under IL-2 chronic therapy. Future studies should also investigate whether IL-2 might be a useful complement to classical treatments, at least for selected patients.[11,12]

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