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Low-Dose Interleukin-2 for Treating Postautologous Transplant Cytogenetic Abnormality Recurrency in a Case of Acute Myeloid Leukemia With Hyperdiploidy

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Low-Dose Interleukin-2 for Treating Postautologous Transplant Cytogenetic Abnormality Recurrency in a Case of Acute Myeloid Leukemia With Hyperdiploidy

To the Editor:

Adoptive immunotherapy and/or immunostimulation may be effective in treating early phases of leukemia relapsing after allogeneic transplant. Donor lymphocyte infusion (DLI) is an established treatment for cytogenetic relapse of chronic myeloid leukemia (CML) after unmanipulated or T-cell–depleted bone marrow transplant (BMT)[1]; favorable results have also been reported in a few cases of initial posttransplant relapse of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).[2] A graft-versus-leukemia (GVL) effect as part of a manifest or occult DLI-elicited graft-versus-host disease (GVHD) is thought to be the reason for these favorable results. For patients who had received autologous transplant, attempts to elicit an antineoplastic effect by immunostimulation have been made using in vitro interleukin-2 (IL-2)–activated autologous lymphocytes and/or IL-2 in vivo administration.[3,4] We report on the successful use of subcutaneous (sc) low-dose IL-2 in a patient suffering from AML with recurrence of cytogenetic abnormalities after autografting.

A 56-year-old woman received diagnosis of AML French-American-British (FAB) M1 in October 1995. Hemoglobin (Hb) level was 6.7 g/dL, platelet count 52×10^9/L, white blood cell count 4.3×10^9/L, with 46% blast cells. A bone marrow (BM) aspirate showed 90% medium-large sized leukemic blasts with immunophenotype $CD13^+$, $CD33^+$, $CD34^+$, $HLA\text{-}DR^+$. Cytogenetic analysis on 24-hour cultured BM cells showed a hyperdiploid karyotype in 10 of 10 metaphases, with 8 near-triploid clones (chromosome count: 71,71,71,72,72,73,75,75), having a common core XXX +1,+2,+3,+4,+5,+6,+7,+7, +8,+9, +10,+11,+12,+13,+14,+15,+15,+16,+20,+21,+22. The patient was induced into complete remission (CR) with the EORTC-GIMEMA AML-10 protocol, and received the scheduled consolidation course with some delay for a pulmonary infection. In March 1996 stem cells were mobilized by glycosylated recombinant human granulocyte colony-stimulating factor (rhG-CSF) 10 μg/kg/d for 5 days and 2.2×10^6/kg $CD34^+$ cells were collected from peripheral blood by four aphereses. Autograft was performed in May 1996, after conditioning with BAVC (carmustine 800 mg/m^2 day −6, VP-16 150 mg/m^2 days −5 to −3, cytarabine 300 mg/m^2 days −5 to −3, amsacrine 150 mg/m^2 days −5 to −3). Hematological recovery was excellent and the patient was discharged on day +20. Complete immunological reconstitution (normal natural killer [NK] cells and CD4/CD8 ratio) was documented 8 months after transplant. The patient remained in hematological and cytogenetic (46 XX) CR until May 1997, when macrocytosis (mean corpuscular volume [MCV] 105 fL) and moderate thrombocytopenia (70×10^9/L) appeared. BM showed moderate trilinear dysplasia without blast excess by morphology and flow cytometry; at that time NK cells and CD4/CD8 ratio were decreased. Cytogenetic analysis revealed a hyperdiploid karyotype (66-72 XXX) in 6 of 12 metaphases with the same chromosomal abnormalities as at diagnosis. Because there were no other signs of leukemia relapse, in July 1997 we started an outpatient-based treatment with low-dose recombinant IL-2 (Proleukin; Chiron, Emeryville, CA), 0.9 MU/m^2 sc 4 days a week. Three months later, the hyperdiploid clone was no longer detectable in BM (46 XX in 12 of 12 metaphases). In October 1998 she was still leukemia free, with a normal karyotype (46 XX in 15 of 15 metaphases) and persistence of dysplasia (MCV 108 fL, platelet count 69×10^9/L). Tolerance to IL-2 was excellent, with a normal quality of life; no eosinophilia was observed. NK cells (especially the subset $CD122^+$) increased, and CD4/CD8 ratio rapidly returned to normal. Thus, even a prolonged administration of low-dose IL-2 seems sufficient to produce a measurable immunostimulation. IL-2 treatment was stopped after 1 year.

IL-2 has been used in recent years as maintenance treatment of AML patients, with discordant results[5,6]; the drug was usually ineffective in relapsed or refractory AML patients, when the blast cell burden was high; whereas encouraging results were observed in a few patients with low tumor burden. High intravenous doses by continuous infusion were generally used, causing severe side effects and poor compliance to the treatment. In a controlled trial with short infusion of high-dose IL-2 for 2 months in AML patients autotransplanted in first CR, no advantage was found on the probability of relapse.[7] We have used low doses of IL-2 for a prolonged period of time without any side effects; this treatment was followed by reversion of the recurrent cytogenetic abnormalities.

Hyperdiploidy is reported in 10% to 20% of childhood ALL and seems to be associated with good prognosis; it is a rare finding in AML.[8] No report on the association between hyperdiploidy and dysplasia is present in the literature; in our patient, hyperdiploidy and dysplasia were probably expressions of different phenomena. Dysplasia was probably a late effect of the previous chemotherapy: it was absent at diagnosis, and persisted at relapse even after disappearance of hyperdiploidy. The absence of BM blastosis at cytogenetic relapse is puzzling. We may surmise that in our patient the hyperdiploid clone was not the actual leukemic clone, but rather a preleukemic expansion of an (n-1) population from which leukemia emerged. Even if this is the case, the immunological control of the (n-1) clone may be of paramount importance in preventing leukemia relapse. Finally, it is possible that different forms of leukemia may have different sensitivity to an immunological treatment, depending essentially on cell-surface alterations that can be recognized by activated lymphocyte subsets. In this setting, a hyperdiploid clone might be a better target for an immunological attack, because cells may have an increased number of surface molecules. Thus, it may well be that immunologic treatment of a low-burden acute leukemia has selected indications, which are still to be defined.

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Expression of AC133, a Novel Stem Cell Marker, on Human Leukemic Blasts Lacking CD34$^-$ Antigen and on a Human CD34$^+$ Leukemic Cell Line: MUTZ-2

To the Editor:

A novel hematopoietic stem and progenitor cell marker, monoclonal antibody (MoAb) AC133, was recently published by Miraglia et al[1] and Yin et al[2] in the December 15, 1997 issue of *Blood*. AC133 recognizes only CD34 bright and CD38$^-$ subsets of human progenitor cells including colony-forming unit granulocyte macrophage (CFU-GM) needed for short-term engraftment and probably the severe combined immunodeficient (SCID) mouse repopulating cell.[3] Investigators could detect AC133 in a majority of CD34$^+$ cases of acute leukemia, suggesting that it may be an early marker for human progenitor cells. In contrast, they could not detect AC133 in the CD34$^-$ leukemic blasts of 1 patient with acute myelogenous leukemia (AML) or in any of 5 human AML cell lines, although expression was found in 3 nonhematopoietic cell lines of human origin.

We investigated several human cell lines by multiparameter immunophenotyping using AC133-PE (Miltenyi, Bergisch Gladbach, Germany) and CD34-Cy5, CD90-FITC (Immunotech, Marseille, France). We found that a majority of cells of MUTZ-2 coexpressed CD34 and AC133 (Fig 1). Mutz-2 is a cell line derived from AML and displays an FAB:M2 morphology.[4] This is the first known human hematopoietic cell line expressing AC133, representing a possible additional tool for experiments concerning the function of the AC133 receptor.

We also characterized expression of CD34 and AC133 in bone marrow blasts from 10 patients with AML. None of the six patients with a pure CD34 negative blast population had detectable levels of AC133$^+$ blasts. On the other hand, we saw a 53-year-old male AML patient with blasts of FAB:M4 morphology and a high percentage of bone marrow infiltration (>90% leukemic blasts) who had a mixed population of CD34$^+$ and CD34$^-$ blasts (Fig 2). As expected, we found coexpression of CD34 and AC133 in 44% of the blast population. Only a very small population of leukemic blasts was AC133$^-$ and CD34$^+$. Interestingly, we could find a significant blast population (18%) in which expression of AC133 was not accompanied by expression of CD34 or CD90 (Thy-1). This first report of a CD34$^-$CD90$^-$AC133$^+$ leukemic blast population could represent clonal diversity of the blast population. On the other hand, it may suggest a possible differentiation pathway, wherein CD34$^-$CD90$^-$AC133$^+$ cells give rise to CD34$^+$AC133$^+$ cells. Alternatively, the CD34$^+$AC133$^+$ blasts could be progenitors of the CD34$^-$AC133$^+$ cells seen in this patient. Therefore, our finding of a CD34$^-$AC133$^+$ blast population raises questions about the significance of AC133 expression in AML. A more detailed investigation of the role of AC133 in AML differentiation pathways needs to be done.

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