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Case reports

Transient complete remission of acute lymphoblastic leukemia in relapse after allogeneic bone marrow transplantation induced by donor leukocyte transfusions

L D' Hondt[1], C Chatelain[1], C Doyen[1], JC Osselaer[1], A Ferrant[2] and A Bosly[1]

[1] Services d'Hématologie et de Biologie Clinique, Clinique Universitaire de Mont-Godinne, B-5530 Mont-Godinne, Belgium
[2] Service d'Hématologie, Cliniques Universitaires Saint-Luc, B-1200 Brussels, Belgium

Abstract. We report the case of a young patient with refractory acute lymphoblastic leukemia relapse, after allogeneic bone marrow transplantation, who was treated by donor leukocyte infusions. We observed potent adoptive immunotherapy which produced a cytologic complete remission and total chimeric state. This was of short duration and the patient died of severe graft-versus-host disease. We present a short summary of the literature concerning acute lymphoblastic leukemia and donor leukocyte infusions.

Rémission complète transitoire d'une leucémie lymphoblastique aiguë, en rechute après greffe de moelle allogénique, obtenue par l'administration de leucocytes provenant du donneur

Résumé. Nous rapportons le cas d'un jeune patient souffrant d'une rechute réfractaire de leucémie lymphoblastique aiguë, après transplantation médullaire allogénique, traité par l'administration de leucocytes provenant du donneur. Nous avons observé l'apparition d'une immunothérapie adoptive efficace avec obtention d'une rémission complète cytologique et un état de chimérisme complet.La rémission complète a été de courte durée et le patient est décédé de réaction du greffon contre l'hôte sévère. Nous présentons un bref résumé de la littérature concernant la leucémie lymphoblastique aiguë et son traitement par l'administration de leucocytes provenant du donneur.

Correspondence to: L D'Hondt, Service d'Oncologie, Cliniques Universitaires Saint-Luc, B-1200 Brussels, Belgium

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Leukemic recurrence after high-dose chemotherapy (HDC) and allogeneic bone marrow transplantation (BMT) constitutes a major therapeutic problem. Attempts have been made to induce a graft versus leukemia (GVL) effect by infusing mononuclear cells (MNC) of donor origin. Some encouraging results have been obtained in CML, with prolonged cytologic and cytogenetic CR [1-4]. This therapy has rarely been used in acute lymphoblastic leukemia (ALL) [5] and the results are controversial [2], although several reports suggest the possibility of a favorable effect [6]. We used this treatment in a patient with second ALL relapse after allogeneic BMT.

Case report

A young male patient born in 1975 was referred in September 1990 for acute leukemia. Bone marrow aspiration showed massive infiltration by ALL and was classified as L2, early pre-B. The patient received chemotherapy and achieved complete remission (CR). HDC consisting of cyclophosphamide and TBI followed by allogeneic BMT from his HLA matched sister was performed in March 1991 without any serious complications. No graft-versus-host disease (GvHD) was observed. In September 1991, there was a bone marrow leukemic relapse. A second CR was obtained with chemotherapy. In January 1993, there was a second blood and bone marrow relapse with mixed chimerism. The disease was resistant to chemotherapy. The patient showed profound neutropenia and thrombocytopenia. In April 1993, we transfused fresh leukocytes from his sister. MNC

were harvested by a FENWALL CS 3000 apheresis system. A total dose of 5 x 10^8 MNC (T cell determination not available) was infused daily during four consecutive days. At day 5 after infusion we observed a significant increase in the WBC count, predominantly neutrophils. These cells were of donor origin as determined by the presence of 2 X chromosomes. The WBC count peaked at 40,000/mm^3 at day 9 after infusion and then progressively decreased to reach a normal and sustained value at day 18.The platelet count progressively improved and became normal at day 25. Bone marrow aspiration performed on day 30 displayed 4% blast cells. Six weeks after the infusions, the patient developed grade III cutaneous, intestinal and hepatic GvHD. The blood cell count deteriorated with mild neutropenia and progressively severe thrombocytopenia, necessitating platelet transfusions. Methylprednisolone, cyclosporine A and anti-thymocyte globulins were administered. Two bone marrow aspirations performed in June and July displayed cytologic CR and complete chimerism. Despite treatment, the GvHD progressed and led to the patient's demise at the end of August 1993. Post-mortem bone marrow aspiration displayed florid relapse.

Discussion

This case illustrates a transient (5 months) cytologic CR with complete chimerism, induced by fresh donor leukocyte infusions, of a second chemoresistant ALL L2 relapse after allogeneic BMT. The results of this procedure in the setting of acute leukemia are disappointing. For relapsed AML, CR can be obtained in only 29% [2], and results for ALL are poorer. In a recent report, Kolb et al [2] described 22 patients with ALL treated by donor leukocyte infusions; 21 were evaluable. Twelve were treated in relapse after allogeneic BMT. No remission was obtained. In 9 patients, this procedure was used as a consolidation of chemotherapy-induced CR. The donor leukocyte infusions failed to maintain CR in 6 patients. Others [5] reported 3 patients with relapsed ALL treated by donor leukocyte infusions. One obtained CR but developed grade IV GvHD and died 5 months later.

The case reported here presents several peculiar features. The first one is the tremendous increase in the WBC count 5 days after the infusions. Leukocytes were of donor origin and were predominantly neutrophils.

The second is the rapid improvement and normalization of the hemogram; the WBC count was normal after 18 days and the platelet count was restored after 25 days.

The third is that the cytologic CR, confirmed twice by bone marrow aspirations, appeared only after the development of clinical symptoms of GvHD. The GvHD was particularly severe and resistant to the treatments tried. The patient eventually died of GvHD.

The fourth is that CR was obtained despite the high tumor cell burden. Some authors have emphasized the importance of a low tumor burden in order to allow a maximal effect of adoptive immunotherapy [7]. Others point out the importance of a defined T-cell dose infused to the recipient to obtain a favorable GVL effect in the absence of clinical GvHD [8-9].

The fifth is the florid leukemic relapse displayed by post-mortem bone marrow aspiration. A possible explanation for this fact is the hypothesis that the decreased expression of HLA antigens and absence of costimulatory factors permit leukemic cells to escape the GVL reaction [2].

In conclusion, this case illustrate a transient favorable GVL effect induced by donor leukocyte infusions in a patient with chemoresistant ALL L2 relapse after allogeneic bone marrow transplantation. A cytologic CR with complete chimerism was obtained. Unfortunately, the patient died of GvHD and post-mortem bone marrow examination displayed florid leukemic relapse.

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