CONCISE REPORT

Restoration of Normal Hematopoiesis by Bone Marrow Ablation and Allogeneic Marrow Transplantation in a Case of Hodgkin's Disease Therapy-Related Preleukemia

By Martin Gyger, Claude Perreault, Jacques Boileau, Jean-Pierre Aymard, Yvette Bonny, Michel Lacombe, René Lavallee, Giovanni d’Angelo, and Elie Tawil

Therapy-related leukemias are generally preceded by a preleukemic phase of several months duration, characterized by pancytopenia, abnormal bone marrow findings, and nonrandom chromosomal abnormalities in almost all cases. No specific therapeutic guidelines are recommended in this preleukemic phase or any other type of preleukemia; aggressive combination chemotherapy is usually withheld until the full expression of leukemia. A 22-yr-old man with therapy-related preleukemia following treatment of Hodgkin’s disease received as primary treatment ablative chemotherapy followed by marrow transplantation from his histocompatible sister. At day 316, the patient is still in complete bone marrow recovery with a normal donor karyotype. In the light of the very poor results obtained with conventional chemotherapy regimens once the leukemic phase is established, we suggest that bone marrow transplantation, if undertaken before leukemic conversion, may be the treatment of choice in young adults with therapy-related preleukemia.

IT IS NOW well established that patients potentially cured of Hodgkin’s disease, mostly those treated with combined modality regimens using alkylating agents and radiotherapy, are susceptible to the occurrence of secondary leukemias; acute nonlymphocytic leukemia (ANLL) is by far the most predominant type of secondary leukemia in such instances. Many of these therapy-related ANLL are preceded by a preleukemic phase characterized by the appearance of pancytopenia, anisopikilocytosis, and sometimes, nucleated red blood cells in peripheral blood. Bone marrow aspirations and/or biopsies are always abnormal, and cytogenetic studies have shown nonrandom chromosomal abnormalities in almost all of these preleukemic patients. These clinical, hematologic, and cytogenetic features are referred to as therapy-related preleukemia (TRPL) or therapy-related preleukemic syndrome, which is also found in patients treated for a variety of malignant and nonmalignant disorders. Aggressive therapy is usually withheld until frank leukemia is established. We report the case of a patient that was successfully treated with bone marrow ablation followed by allogeneic marrow transplantation before the full clinical and hematologic expression of leukemia and discuss the role of bone marrow transplantation in TRPL.

CASE REPORT

A 22-yr-old man presented in October 1979 with a history of increasing fatigue. Physical examination and hematologic parameters were unremarkable. Pulmonary x-ray showed a large mediastinal mass, which proved to be nodular sclerosis Hodgkin’s disease on biopsy specimens. Clinical staging procedures revealed the patient to be stage IIIA. Complete remission was achieved following two cycles of MOPP chemotherapy and total nodal irradiation.

From August 1981 to January 1982, hematologic parameters showed a progressive bicytopenia involving the red cell line and granulocytes. By January 1982, the absolute neutrophil count was 532/μl, hemoglobin 8.6 g/dl. Posterior iliac crest marrow aspirates and biopsies were hypocellular; no excess blast or sideroblastic changes were noted. Myelofibrosis, Reed-Sternberg cells, and granulomas were absent in marrow biopsy specimens. Other laboratory features included increased fetal hemoglobin (6.1% by the alkaline denaturation test) and normal serum B-12 and folate levels. Extensive clinical investigation did not reveal any evidence of relapsing Hodgkin’s disease. Chromosomal studies were made at three different intervals. On two occasions, the studies were unsuccessful because of severe hypoplasia of marrow aspirates. Seventeen metaphases were analyzed using standard Giemsa banding technique. The karyotype was as follows: 46,XY./45,XY.–13/44,XY.–13,–random changes. In all, 9 cells were monosomic for chromosome no. 13.

In March 1982, reassessment of bone marrow status by aspirate and biopsy did not reveal any signs of leukemic conversion. The patient was then prepared for bone marrow transplantation with busulfan (4 mg/kg on days –8 to –5) and cyclophosphamide (50 mg/kg on days –4 to –1). On day 0, he received 2.6 x 10⁹ marrow cells/kg from his ABO and HLA-identical, mixed lymphocyte culture compatible sister. Regular graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate, 15 mg/sq m on day 1, 10 mg/sq m on days 3, 6, 11, and then weekly after the first 100 days posttransplantation. The postgraft period was complicated by an episode of interstitial pneumonia with severe hypoxemia (P_0₂ 54 mmHg) at day 154. Examination of lung tissue obtained by transbronchial biopsy revealed histopathologic features suggestive of myleran and/or cyclophosphamide toxicity (Fig. 1A and B); special stains for pneumocystis carinii were negative. High-dose steroid therapy resulted in prompt but partial improvement of the pulmonary status (P_0₂ 65 mmHg). At day 316, the patient is still in...
Fig. 1. Transbronchial biopsy showing histological features suggestive of myleran and/or cyclophosphamide toxicity (A: x200; B: x500).

There has been substantial improvement in survival and disease-free survival in most stages of Hodgkin's disease over the last decade.8 The general enthusiasm has been somewhat shattered, however, in the past few years by the troublesome rise in therapy-related ANLL, mostly in patients treated with combined modality regimens using radiotherapy and alkylating agents.9 A recent 10-yr survey from Copenhagen has shown a cumulative probability of leukemic complication of 3.9% ± 1.3% 5 yr after the start of treatment and 9.8% ± 2.9% at 9 yr, if estimated according to the Kaplan-Meier method.10 Most of these secondary leukemias are preceded by a preleukemic phase characterized by unexplained cytopenia or pancytopenia; bone marrow studies will reveal a variety of cytologic and histologic abnormalities, including dysplasia, hypoplasia, and aplasia.11-13 Cytogenetic studies using Giemsa banding techniques without methotrexate synchronization will show nonrandom chromosomal aberrations in almost all of these patients,14 compared to approximately half of the patients with other preleukemic states.15-17

This preleukemic phase may last from a few months to almost 2 yr, ANLL being the terminal event in the majority of the cases.18 This is a critical period where one usually Withholds aggressive combination chemotherapy and where the patient is exposed to fatal hemorrhagic or infectious complications before the onset of leukemic conversion because of profound thrombocytopenia or neutropenia. Once the full hematologic and clinical expression of leukemia is established, results of conventional chemotherapy are very poor. Complete remission rates in the range of 60%-80% are now regularly achieved in “de novo” ANLL,19 20 with 15%-30% of these complete responders becoming long survivors.21,22 The average complete remission rate in therapy-related leukemia is approximately 10%,23,18,23 and very few long survivors have been reported.24 To our knowledge, two patients previously treated for Hodgkin's disease with ANLL have received an HLA-identical bone marrow transplantation. Both patients were grafted during the leukemic phase of this disease and died in the early posttransplant period.2,25

Patients treated for Hodgkin's disease, compared to patients with other malignancies, make up a distinct subset of patients carrying an increased risk of developing ANLL. Indeed, Hodgkin's disease is the most
common primary neoplasm associated with secondary leukemia in children, and many adult patients at initial diagnosis of preleukemia are in the age range of receiving a graft. Also, a large number of patients are likely to receive combined modality regimens in many centers. Finally, in view of the fact that most patients treated for Hodgkin's disease are probably cured of their disease, the rise in therapy-related leukemia may affect the overall survival curve. Early recognition of TRPL is highly important in view of the fact that allogeneic bone marrow transplantation is of little therapeutic benefit in patients with advanced leukemia or leukemic relapse. Allogeneic marrow transplantation has already shown promising results in chronic myelogenous leukemia if undertaken before blast crisis, other preleukemic disorders with nonrandom chromosomal aberrations, especially those affecting children with repeated infectious episodes, would probably benefit from early bone marrow transplantation.

REFERENCES
Restoration of normal hematopoiesis by bone marrow ablation and allogeneic marrow transplantation in a case of Hodgkin’s disease therapy-related preleukemia

M Gyger, C Perreault, J Boileau, JP Aymard, Y Bonny, M Lacombe, R Lavallee, G d'Angelo and E Tawil