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Successful Allogeneic Bone Marrow Transplantation After Reversion to Chronic Phase of Blast Crisis in Chronic Myeloid Leukemia

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A female with chronic myeloid leukemia (XX Ph 1 +) in blast crisis (localized to pleura and lymph nodes) was treated by polychemotherapy. After reversion to the chronic phase, an allogeneic bone marrow transplantation (BMT) was performed. Sixteen months after BMT, no sign of the disease was present (XY Ph 1 −).

Key words: bone marrow transplantation, chronic myeloid leukemia, blast crisis

INTRODUCTION

Blast crisis (BC) of chronic myeloid leukemia (CML) is most often rapidly fatal. Reversion of the disease to its chronic phase is infrequent and rarely lasts more than a few months. Bone marrow transplantation (BMT) attempts during BC are characterized by high mortality rate as well as the risk of blastic recurrence [1]. We present the first case of successful allogeneic BMT accomplished after reversion to the chronic phase of BC. Sixteen months later, no sign of disease was present, and no cells with Philadelphia chromosomes (Ph 1) were observed.

CASE REPORT

CML was diagnosed in February 1977 in a 22-year-old female patient presenting with 80×10^9/white blood cells per liter with myelemia. Clinically, no splenomegaly, hepatomegaly, or enlarged lymph nodes were found. Treatment consisted of busulfan.

The patient was hospitalized in our department in March 1978 with a poor general condition, weight loss, and fever. Clinical examination revealed: left supraclavicular lymph nodes 4 cm in diameter, bilateral pleural effusion, and no hepatosplenomegaly. Lymphoangiography discovered enlarged, lacunar lumbar-aortic lymph nodes. Cytological examination of lymph nodes and of pleural fluid showed large blastic cells that had no granules

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and that were peroxidase-negative under optic and electron microscopy [2]. Blood and marrow samples showed the features of chronic myeloid leukemia in its chronic phase. Karyotype analysis revealed Ph 1 in all mitoses of marrow cells. Localized pleural and lymph node BC was diagnosed. Polychemotherapy* was started in May 1978 and resulted in disappearance of all clinical and roentgenographic manifestations within two months. The same therapy was maintained monthly for one year.

The patient had no symptoms, except the persistance of Ph 1, when a BMT was carried out August 1979 with her brother's marrow, HLA-identical, nonreactive in mixed lymphocyte culture. Preparation regimen consisted in cyclophosphamide administered for two days: 60 mg/kg (days −5 and −4) followed by total body irradiation using 800 rads with pulmonary protection above 400 rads (day −1). The patient received 4×10^8 bone marrow cells/kg. Daily irradiated white blood cell transfusions were given for a period of 19 days. The graft was rapidly functional, and the patient left the hospital 30 days later. She received a weekly treatment consisting of methotrexate, 10 mg/m^2, for 100 days. No further chemotherapy was given. Sixteen months after BMT, blood and marrow samples were normal, there was no sign of graft-versus-host disease (GVHD), and normal activity was resumed. Marrow karyotypes obtained 27, 46, 180, 360, and 470 days after grafting revealed the sole existence of XY cells lacking Ph 1. Lymphocytic karyotypes showed only XY cells.

DISCUSSION

BC in CML has a very poor prognosis. Reversion to the chronic phase is difficult to obtain with polychemotherapy and is of short duration [3]. Marrow cryopreservation in the chronic phase permits more intensive therapy, total body irradiation, and autograft, but no disappearance of the Ph 1 cells [4]. This, in contrast, may be expected in syngeneic and allogeneic marrow grafts following intensive chemotherapy and total body irradiation. However, BMT attempted during BC in frail patients with a large blastic mass is followed by a high death rate due to infection and a high recurrence rate [1]. As previously established in acute myeloid leukemia, these complications are much less frequent when BMT is performed during complete remission [5]. These observations should encourage BMT in the chronic phase of CML. Thus, successful BMT has already been accomplished in syngeneic conditions and resulted in the disappearance of Ph 1 cells [6]. Under allogeneic conditions, however, the risk of severe infection and GVHD must be put in balance against the possible course of the chronic phase, the duration of which cannot be predicted.

The present case is privileged since BC was localized in the pleura and lymph nodes, and in addition, the blasts were of the so-called "lymphoblastic" type. This may explain the prolonged success of the polychemotherapy. We have in fact treated 30 patients with BC by such a chemotherapy; ten of which returned to a chronic phase. The median survival of these ten patients was ten months (manuscript in preparation). Preparation of the patient for BMT was identical to that usually applied in acute myeloid leukemia during complete remission [7]. Lung shielding was done because of the fear of interstitial pneumonitis, all the more likely since the patient had already received busulfan and heavy doses of CCNU.

*A and B monthly alternate regimen: Regimen A – vincristine (1 mg/m^2) on days 1 and 2; CCNU (60 mg/m^2) on days 3 and 4; cyclophosphamide (300 mg/m^2) on days 3, 4, and 5, prednisone (45 mg/m^2) from day 1 to day 10. Regimen B – adriamycin (45 mg/m^2) on day 1, VM26 (60 mg/m^2) on day 2, cyclophosphamide (300 mg/m^2) on days 3 and 4, prednisone (45 mg/m^2) from day 1 to day 10.

The absence of Ph 1 cells more than 16 months after marrow grafting raises the problem of definite cure. This in itself is a major reason for applying an aggressive chemotherapy as a treatment of accelerations or BC of CML, hoping to perform a BMT using a preferably HLA-identical or even non-HLA-identical siblings once remission is obtained [8].

The repetition of such successes may ultimately encourage the grafting attempts in CML patients during the chronic phase.

REFERENCES

1. Doney K, Buckner CD, Sale GE, Ramberg R, Boyd C, Thomas ED: Treatment of chronic granulocytic leukemia by chemotherapy, total body irradiation, and allogenic bone marrow transplantation. Exp Hematol 6:738, 1978.
2. Marie JP, Vernant JP, Dreyfus B, Breton-Gorius J: Ultrastructural localization of peroxydases in "undifferentiated" blasts during the blast crisis of chronic granulocytic leukemia. Br J Haematol 43: 549, 1979.
3. Coleman M, Silver RT, Pajak TF, Cavalli F, Rai KR, Kostinas JE, Glidewell O, Holland JF: Combination chemotherapy for terminal-phase chronic granulocytic leukemia: Cancer and leukemia group B studies. Blood 55:29, 1980.
4. Buckner CD, Stewart P, Clift RA, Fefer A, Neiman PE, Singer J, Storb R, Thomas ED: Treatment of blastic transformation of chronic granulocytic leukemia by chemotherapy, total body irradiation, and infusion of cryopreserved autologous marrow. Exp Hematol 6:96, 1978.
5. Thomas ED, Buckner CD, Clift RA, Fefer A, Johnson FL, Neiman PE, Sale GE, Sanders JE, Singer JW, Shulman H, Storb R, Weiden PL: Marrow transplantation for acute nonlymphoblastic leukemia in first remission. N Engl J Med 301:597, 1979.
6. Fefer A, Cheever MA, Thomas ED, Boyd C, Ramberg R, Glucksberg H, Buckner CD, Storb R: Disappearance of Ph 1 positive cells in four patients with chronic granulocytic leukemia after chemotherapy, irradiation, and marrow transplantation from an identical twin. N Engl J Med 300:333, 1979.
7. Vernant JP, Rodet M, Rochant H, Feuilhade F, Bierling P, Bracq C, Mannoni P, Dreyfus B: Bone marrow transplantation during the first complete remission of acute myeloid leukemia. 18th Congr Int Soc Hematol, Montreal, 1980.
8. Clift RA, Hansen JA, Thomas ED, Buckner CD, Sanders JE, Mickelson EM, Storb R, Johnson FL, Singer JW, Goodell BW: Marrow transplantation from donors other than HLA-identical siblings. Transplantation 28:235, 1979.