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CASE REPORT

Salvage Chemotherapy with Donor Lymphocyte Infusion and STI 571 In a Patient Relapsing with B-Lymphoblastic Phase Chronic Myeloid Leukemia after Allogeneic Bone Marrow Transplantation*

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Relapse is the main cause of treatment failure following hematopoietic stem cell transplantation for blastic phase chronic myeloid leukemia. Treatment options including donor lymphocyte infusion, second transplantation, interferon- and re-induction chemotherapy are often unsuccessful. We report a patient with blastic phase chronic myeloid leukemia relapsing after allogeneic stem cell transplantation. The post-transplant leukemia was characterized with B-lymphoid markers and multiple genetic abnormalities including double Ph-chromosomes. The disease was treated with three courses of salvage chemotherapy combined with donor lymphocyte infusion and bcr-abl tyrosine kinase inhibitor. The leukemia proved to be non-responsive both to immune therapy and STI 571. The presented case demonstrates the need for combination approaches in post-transplant relapsed leukemia and discusses the possible contributing mechanisms of STI-571 resistance. (Pathology Oncology Research Vol 9, No 2, 131–133, 2003)

Keywords: CML, blastic phase, allogeneic HSCT, DLI, STI 571

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-identical sibling donor is the treatment of choice for patients with chronic phase chronic myeloid leukemia (CML). However, patients undergoing transplantation for blastic phase (BP) CML have a very poor post-transplant survival originating from the high rates of post-transplant relapse and transplant-related mortality.[8] CML patients transplanted in more advanced disease and relapsing after allogeneic HSCT have few therapeutic options, including donor lymphocyte infusion (DLI), second HSCT and the novel bcr-abl kinase inhibitor STI 571 (imatinib mesylate, Glivec).[4,6] Results with DLI in more advanced CML or in acute leukemia are disappointing, probably because of the high proliferation capacity of blast cells and the delayed antileukaemia effect of DLIs.[1,2] Consequently, the need for new therapeutic strategies such as signal transduction inhibitors (STI's) or methyltransferase enzyme inhibitors are obvious.[6,7] STI 571 selectively inhibits bcr-abl tyrosine kinase activity and has excellent effect in chronic CML.[3] In contrast, the patients with myeloid or lymphoid blast crisis show a substantially lower complete hematologic remission and cytogenetic response rate to STI 571.[3] However, combination of STI 571 with bulk dose or escalating dose DLI may improve the outcome of blastic phase relapsed disease. We report a patient with lymphoid BP-CML relapsing after allogeneic HSCT. He received 3 courses of salvage chemotherapy combined with DLI without any effect. Finally, he was treated with STI 571. Despite the combined therapeutic modalities the leukemia did not respond and the patient died from progressive disease on day 309 post-transplant.

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Case report

A 48 year old man was diagnosed with Ph chromosome positive CML in lymphoid BP in July 2000. The peripheral blood (PB) and the bone marrow (BM) histology

showed CML with more than 60% blasts with atypical morphology. The BM mononuclear cells expressed CD34, TdT, CD19, CD20, CD10 lymphoid and CD13 myeloid antigens. The detection of surface CD33 and CD14 antigens and intracytoplasmic myeloperoxidase proved to be negative. Based on immunophenotyping, the blast cells were determined as precursor B-lymphoblasts with aberrant CD13 myeloid marker expression. The BM karyotype showed 100% Ph+ chromosomes. The reverse transcription-PCR (RT-PCR) analysis of the bcr-abl region revealed 100% b2a2 type chimeric transcripts. No clonal rearrangement of the Ig-heavy-chain gene was detected. The patient was treated with the Hoelzer induction protocol and a 2nd chronic phase was achieved.

In 14 November 2000, during his 2nd chronic phase CML he underwent an allogeneic HSCT. The conditioning regimen consisted of total body irradiation (12 Gy) and cyclophosphamide (60 mg/kg x 2). The donor was his HLA-identical, MLC non-reactive brother. Cyclosporin A and short course of metothrexate were administered for prevention of graft-versus-host disease (GVHD). He achieved a complete hematologic and molecular remission documented by negative result of RT-PCR analysis of the bcr-abl gene product. Based on the short tandem repeat analysis of PB cells with two microsatellite markers (chromosome 3 marker for locus D3S3045, chromosome 17 marker for locus D17S1290) complete, donor-type chimerism was documented. The cyclosporin A was tapered after two months. Three months after the transplantation he relapsed with lymphoid blastic leukemia. The BM biopsy showed 100% lymphoblasts with an immunophenotype almost identical with the initial pre-transplant pattern, but lacking the CD13 antigen expression. Conventional cytogenetic analysis (47, XY, t(9;22), +der 22, t(9;22), -1, -6, -7, +mar1, +mar2, +mar3) revealed multiple genetic abnormalities including presence of a double Ph chromosome.

After chemotherapy consisting of fludarabine, Ara-C, G-CSF and idarubicin (FLAG-Ida) he achieved second post-transplant complete remission clinically and morphologically. However, FISH analysis confirmed 30% double Ph chromosomes and RT-PCR documented 10% b2a2-type bcr-abl chimeric transcripts. To further consolidate the remission and eliminate the minimal residual disease, escalating dose DLI from the original donor was introduced without GVHD prophylaxis. The patient received the first DLI with $1x10^7$/kg of CD3+ T-cells from a single leukapheresis session on 3 May 2001. However, within 1 month after the first DLI a second post-transplant relapse developed. After a new course of chemotherapy with Ara-C ($2g/m^2$, days 1-4), the second DLI, containing $1x10^8$/kg CD3+ T-lymphocytes, was infused. There was no evidence of acute GVHD. Unfortunately, at the time of cell recovery the BM contained 50% lymphoblasts again. The third DLI with $1x10^8$/kg of CD3+ T-cells was given after VP-16 chemotherapy (150 mg/m^2, days 1-5). 23 days later the blasts re-appeared again in the blood. Because of the progressive leukemia, treatment was completed with STI 571 (Glivec). It was supposed that reduction in the proportion of blasts by STI 571 would enhance the efficacy of the delayed antileukemic effect of DLI. Treatment with STI 571 as a sole anti-leukemia agent was initiated with 600 mg p.o. per day on 12 July 2001. There was a rapid decrease (more than 50%) in the PB blasts within a few days, but without complete hematologic remission. The STI 571 was temporarily discontinued on day 32 because of side effects. Three days later, due to increasing of the PB blast cell count, STI 571 was reinitiated at a daily dose of 600 mg. However, the disease subsequently progressed and STI 571 was stopped at day 55. The patient did not respond to a further palliative chemotherapy and died in full leukemia.

Discussion

Blastic phase CML is usually unresponsive to AML-like chemotherapy and the only possible curative therapeutic option to date is the allogeneic HSCT.[7] However, after allogeneic HSCT performed in blast phase CML the 5 year survival rate is only 6% and the probability of relapse at 2 years is approximately 70%.[3,8,9]

The post-transplant relapse is generally due to the recurrence of host leukemia cells, but very rarely might derived from cell of the donor.[5] The prognosis of post-transplant BP relapse is extremely poor with the currently available therapeutic modalities.[7,8] For CML patient relapsing in advanced disease after allogeneic BMT the therapeutic options include DLI, second BMT and more recently STI´s.[4,6] STI 571 has remarkable activity as a single agent in CML lymphoid blast crisis but relapse can occur within a few months implicating resistance of the leukemic cells.[3] Several factors may contribute to development of STI 571 resistance: 1) amplification of the bcr-abl gene; 2) increased expression of the bcr-abl protein without amplification of the gene; 3) activation of bcr-abl independent oncogenic pathways; 4) increased expression of the multidrug resistance protein-1 (MDR1).[3,6]

In the reported case the patient presented with lymphoid BP-CML. He underwent an ALL-type chemotherapy and a subsequent matched allogeneic HSCT. Three months post-transplant an ALL-like relapse was documented. The post-transplant leukemia failed to respond to the chemotherapies combined with DLI and STI-571. In this case the treatment failure of STI 571 might be based on complex genetic abnormalities supporting the theory that other oncogenetic pathways can replace the bcr-abl kinase activity resulting in the survival of leukemic blasts.[3]

The presented case – as an example – demonstrates the need for a combination of different therapeutic approaches in BP CML relapsed post-transplant. It is rational to use STI 571 in combination with standard anti-leukemia agents to improve the outcome of the disease. Independently of the disease outcome in the reported case, the current algorithm for management of patient with CML may soon change according to the maturing results with signal transduction inhibitors. It maybe that STI 571 could replace the DLI administration in early relapse after allogeneic HSCT.

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