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Case Report

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Allogeneic Sibling Donor Peripheral Blood Stem Cells Transplantation With Myeloablative Conditioning for Chronic Myeloid Leukemia in Blast Crisis-Successful Treatment Despite Severe Phase of the Disease

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Abstract

We report a case of a 30-year old patient with Ph-positive chronic myeloid leukemia (CML) in blast crisis in whom short pretreatment with dasatinib was followed by myeloablative conditioning and successful allogeneic hematopoietic stem cell transplantation from HLA-matched sibling-donor. Full donor chimerism has been achieved; no bio-molecular and cytogenetic markers of CML have been detected post-transplant despite lack of further treatment with tyrosine kinase inhibitor. Post-transplant course was complicated by several infections and graft-versus-host disease which were all effectively treated. Patient has limited chronic GVHD and no evidence of CML 20 months after allo-HSCT. Our report proves that successful allo-HSCT can be performed in advanced phase CML and that complete molecular and cytogenetic remission can be maintained post-transplant without further TKI treatment.

Keywords: Chronic myeloid leukemia; Blast crisis; Allogeneic stem cells transplantation

Introduction

Progression of chronic myeloid leukemia (CML) to blast crisis (BC), either myeloblastic, or lymphoblastic, has extremely poor prognosis [1, 2]. Median survival time in patients diagnosed with CML in BC is up to 3 - 6 months. Although imatinib mesylate is regarded to be the most active drug for CML, median survival in blast phase treated with tyrosine kinase inhibitor (TKI) lasts approximately for 7 months. According to recommendations, blast crisis should be treated at first with intensive chemotherapy, following by continuous TKI therapy. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) still remains the only curative option nowadays. Patients with no donor are a group of high risk for rapid relapse. Reported 5-year survival after allo-HSCT from sibling donor is achieved by approximately 15% of patients, from HLA-compatible unrelated donor by 10% of patients [3].

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Case Report

We report a case of sibling-donor allo-HSCT performed in a 30-year old male patient with CML in BC. The diagnosis has been established 3 months prior to transplantation on the base of bone marrow morphology with 34% infiltration of myeloblasts confirmed by flow cytometry, presence of chromosome Philadelphia in 100% metaphases and bcr/abl p210 oncogene in bio-molecular evaluation. Other bio-molecular rearrangements (CBF/MYH-11, RUNX1-RUNX1T1, bcr/abl p190 and FLT3/ITD) were excluded. The initial peripheral blood morphology revealed hyperleukocytosis 203 G/l with 30% of myeloblasts, anemia (hemoglobin 7.5 g/dL and hematocrite 24%) and thrombocytopenia (PLT 30 G/l). Lymphoadenopathy and splenomegaly were detected in initial physical examination.

Cytostatic chemotherapy with Daunorubicin 120 mg/d i.v. (on days 1 - 3) and Ara-C 400 mg/d i.v. (on days 1 - 7) were given as a first line treatment which led to the reduction of hyperleukocytosis followed by regeneration of hematopoiesis. Treatment with second generation TKI - dasatinib, in the initial dose 140 mg/d, started 1 month after chemotherapy. Patient required the reduction of initial dose to 100 mg/d due to cytopenia. The TKI therapy lasted for one month and then patient was admitted to the transplant unit. No remission of disease has been observed prior to start of conditioning treatment (49% myeloblasts were present in peripheral blood smear). The donor was patient's brother, 24 years old, HLA-matched, compatible in HLA-A,B,C,DR,DQ at the level of low resolution typing, compatible in major blood group and Rh antigens with the recipient.

The myeloablative conditioning consisted of busulfan-

16 mg/kg as a total dose administered on days from -11 to -6 (1/3 i.v. and 2/3 p.o.) and cyclophosphamide- 120 mg/kg as a total dose administered on days from -4 to -2. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A- 3 mg/kg/d administered from day -1 and methotrexate 15 mg/m^2 given on day +1 and 10 mg/m^2 given on days +3 and +6. Transplanted peripheral blood apheresis product contained 7.34 x 10^8 nucleated cells/kg, 7.96 x 10^6 CD34+cells/kg and 26.32 x 10^7 CD3+cells/kg.

Mucosistis 2nd grade in oral cavity accompanied by fever was observed during the post-transplant period. No bacterial, viral or fungal pathogens were detected. Agranulocytosis lasted for 14 days, 6 units of filtered erythrocytes, 5 units of single donor platelets and 2 units of fresh frozen plasma were transfused during pancytopenia phase. Regeneration was complete: granulocyte count of 1.0 G/l has been achieved on day +15, absolute neutrophils count (ANC) 0.5 G/l on day +16, platelets count 20 G/L on day +13 and platelets count of 50 G/L on day +14. Acute graft-versus-host reaction grade 1 was present on skin from day +13 with good response to pulse of methylprednisolone administered i.v. Elevated activity of liver enzymes (AspAT, AlAT, GGTP) was detected on day +24, however there was no increase of bilirubin and viral tests (HBV, HCV, CMV, EBV) performed with use of polymerase chain reaction method were negative. Complete 100% donor chimerism (examined with use of short tandem repeat method) has been achieved in the bone marrow on day +24 following allo-HSCT. Neither chromosome Ph nor bcr/abl p210 oncogen presence was revealed by cytogenetic and bio-molecular tests. The patient has been released from the hospital 25 days following allo-HSCT.

On day +40 patients were re-admitted because of dysuria and hematuria, Polyoma BK, Adenovirus and Klebsiella were detected in urine. Throat infection with positive Citrobacter freundii and Enterobacter cloacae was also present. Overmore, aGVHD progressed to grade III (skin- 3, liver- 2), activity of transaminases was still elevated. Patient was treated with cidofovir given in 3 doses and with antibiotics chosen according to pathogens susceptibility profile. Immunosuppressive treatment was modified- ciclosporine was switched to mycophenolate mofetil and steroids.

Five months after allo-HSCT borderline CMV reactivation was detected in PCR method, patient experienced fever at this time. Treatment with ganciclovir 600 mg/d for 14 days was provided with good effect (negativisation of CMV in PCR test).

Seven months after allo-HSCT patient had pulmonary infection manifested by fever and dyspnoea which required hospitalization and treatment with i.v. antibiotics. High resolution computed tomography of thorax (HRCT) showed inflammatory focus in lungs and suspicion of bronchiolitis obliterans (BO), but BO has been not confirmed in spirometry. Health status of patient improved gradually.

At this moment, 20 months after allo-HSCT, patient complains of temporary dysuria and limited chronic GVHD is present on skin. Donor chimerism is 100% and no evidence of CML is present in cytogenetic or bio-molecular evaluation. The patient has not been treated with TKI post-transplant.

Discussion

The approach to CML patients in blast crisis is still controversial.

Effective autologous stem cell transplant strategies may benefit from the availability of cryopreserved autologous product obtained during maximal molecular response, but this procedure is not in routine practice. It was reported that treatment of CML in blast crisis with imatinib combined with high-dose cytarabine and autologous HSCT after high-dose chemo-/radiotherapy may result in complete molecular remission [4].

Combination of imatinib with allo-HSCT from unrelated donor with myeloablative conditioning consisting of total body irradiation, cyclophosphamide and etoposide was reported as a successful treatment of a lymphoid blast crisis in CML [5]. Also promyelocytic blast crisis has been successfully managed with an effective induction regimen followed by allo-HSCT [6]. A patient with lymphoblast crisis CML expressing major and rarely reported minor BCR/ABL transcripts underwent one course of idarubicin and cytarabine induction therapy combined with imatinib, followed by consolidation therapy and subsequent high-dose chemotherapy (total body irradiation and cyclophosphamide) and allo-HSCT from a HLA-matched unrelated donor, what resulted in 19 months disease-free survival [7]. However, the pre-transplant use of imatinib does not influence the results [8], as the vast majority of CML blast crisis cases today arise in patients already on imatinib-based therapy [9]. Second-generation TKI dasatinib or nilotinib may be given as salvage therapy for advanced disease, which should be followed by allo-HSCT, as the progression-free survival in second chronic phase CML after dasatinib administration is limited [10]. It has been reported that in CML blast crisis developed after previous imatinib and nilotinib treatment, a second complete hematological response was achieved with dasatinib, which allowed for allo-HSCT, resulting in complete molecular remission [11]. In another report pre-transplant dasatinib treatment of two CML patients in blast crisis lasting for 8 and 6 months resulted in complete cytogenetic response [12]. Patients transplanted after achieving a second chronic phase with salvage therapy have somewhat better outcome of allo-HSCT [9]. Such strategy cannot be applied in each patient, because with the availability of imatinib, fewer CML patients are being transplanted in the early stages of their disease, and the molecular heterogeneity of blastic phase CML

may limit the durability of treatment regimens based solely on oncogene-targeted therapy. Thus transplanting CML patients with more advanced disease who fail to achieve major or complete molecular and cytogenetic responses have to be challenged. It is unclear whether patients who do not respond to imatinib should receive allo-HSCT immediately or should receive a trial of treatment with a second-generation TKI, this issue is being addressed in ongoing clinical trials. Patients receiving definitive treatment with second-line TKI must be closely monitored with plans for allo-HSCT at the first signs of treatment failure. Treatment with second-line TKI can be initially given for a predetermined period of time to evaluate response. Patients whose disease does not respond optimally to TKI treatment should be referred to allo-HSCT [13].

Our report shows that short dasatinib therapy (one month duration) without obtaining complete hematologic response, followed by allo-HSCT was effective in advanced CML patient. The incidence of relapse reported by others was significantly lower in patients who developed acute or chronic GVHD [14]. Our patient developed acute GVHD grade 3 followed by limited chronic GVHD, and therefore the immune graft-versus-leukemia effect can be expected, and in fact the bcr/abl p210 transcripts were undetectable after the onset of GVHD.

Further accumulation of experience regarding allo-HSCT with optimal pre-transplant TKI is necessary to improve the outcome of CML in the blast crisis. Allo-HSCT remains the most effective anti-leukemic treatment for CML, with the majority of surviving patients achieving molecular complete remission with undetectable bcr-abl rearrangement, what represents superior cytoreduction of the leukemia than can be achieved with TKIs. Our report confirms that the therapeutic effect of allogeneic transplantation with myeloablative preparation in CML blast crisis can be achieved and maintained after allo-HSCT without further administration of TKI.

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