Related Haploidentical Peripheral Blood Stem Cell Transplantation as a Rescue after Double Cord Blood Unit Graft Rejection in an Anti-HLA-Immunized Patient

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Abstract
A reduced intensity conditioned related haploidentical stem cell transplantation was performed as a rescue after an allogeneic unrelated double cord blood units transplantation failure for a secondary myelodysplasia with a large anti-HLA immunization. The conditioning regimen consisted of thiopeta 5 mg/m² on D - 7, fludarabine 40 mg/m² on D - 6 to D - 3, IV busilvex 3.2 mg/m² on D - 6 and D - 5, thymoglobulin 2.5 mg/kg on D - 1. Graft versus host disease prophylaxis started with IV ciclosporin 3 mg/kg and oral mycophenolate mofetyl 1 g twice a day on D + 6 with corticosteroids (1 mg/kg) between D0 and D + 3. A poor graft function was diagnosed in the first three months after the autologous procedure while the patient remained in major molecular response on imatinib. Cytopenias worsened and additional cytogenetic abnormalities were identified with a myelodysplasia international prognostic score (IPSS) reaching 1.5 in July 2014.

Patient and Methods
In September 2014, two 5/6 HLA compatible cord blood units were identified. Reduced intensity conditioning regimen included 2 Gy single dose total body irradiation on D - 7, fludarabine 40 mg/m² from D - 7 to D - 3, cyclophosphamide (Cy) 50 mg/kg on D - 6 to graft versus host disease (GvHD) prophylaxis associated oral cyclosporine A (CsA; 4, 5 mg/kg twice a day) and mycophenolate mofetyl (MMF, 1 g 3 times a day) on D - 3. After thawing and washing, the characteristics of the 1st and 2nd cord blood units were respectively: viability 59 % and 63 %, total CD45 + cells/kg 1.1 × 10⁷ and 1.5 × 10⁷ and CD34 + cells/kg 0.5 × 10⁶ and 0.4 × 10⁶ (total injected of 7.5 and 4.2 × 10⁷ cells/kg). On D + 42, no hematological recovery was observed and we confirmed the lack of any engraftment with a desert marrow aspiration and the absence of any donor chimerism in blood. At the same time a large anti-HLA immunization (anti-HLA-A, -B, -DR, -DQ, -DP and -DP) was highlighted in a context of total platelet-transfusion inefficacy; a strong immunization against each mismatched HLA antigens of the two cord blood units (donor specific antibodies) was identified two days after their infusion (anti-HLA-B7 and -B57). We decided to treat the HLA immunization with two doses of rituximab 375 mg/m² on D + 15 and D + 23, three courses of plasmaphereses on D + 39, D + 41, D + 43 and high dose of intravenous (IV) human immunoglobulins (1 g/kg) once a week for three weeks [1]. The cord blood transplantation was also complicated on D + 10 by a severe BK virus cystitis with macroscopic hematuria, clots in the bladder and acute urine retention. No other infections were documented during this long period of severe aplasia and cystitis was successfully treated with two IV injections of cidofovir 5 mg/kg and two IV injections of 3000 UI of blood coagulation factor XIII [2].

In emergency, with the consent of the patient and the donor, we decided to perform a reduced intensity conditioned related haploidentical stem cell transplantation of peripheral blood stem cell (PBSC) of her son. The conditioning regimen consisted of thiopeta 5 mg/m² on D - 7, fludarabine 40 mg/m² on D - 6 to D - 3, IV busilvex 3.2 mg/m² on D - 6 and D - 5, thymoglobulin 2.5 mg/kg on D - 1. GvHD prophylaxis started with IVCsA 3 mg/kg and oral MMF 1g BID on D - 6, cyclophosphoroids (1 mg/kg) between D0 and D + 5 and IV Cy 50 mg/m² on D + 3 and D + 5 post-transplantation as previously described [3]. PBSCs of the son were injected on D + 65 after the cord blood transplantation. Total infused PBSC counts were 7.2 × 10⁹ CD45 + cells/kg (viability 999 %) and 4.6 × 10⁹ CD34 + cells/kg, Anti-HLA immunization was only weakly decreased in the serum samples tested on the day of this second graft and donor

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Abdomination
CML: Chronic Myeloid Leukemia; IPSS: International Prognostic Score; GvHD: Graft Versus Host Disease; CsA: Cyclosporine A; MMF: Mycophenolate Mofetyl; HLA: Human Leukocyte Antigen; IV: Intravenous; BKv: BK virus; PBSC: peripheral blood stem cell.

Introduction
We describe here a reduced intensity conditioned related haploidentical stem cell transplantation rescue in a 57-year old woman after graft failure of an allogeneic unrelated double cord blood unit transplantation in a context of a large anti-HLA immunization. Stem cell transplantation was indicated for a secondary myelodysplasia post-autologous transplantation for a chronic myeloid leukemia (CML) in first chronic phase and major molecular response. A poor graft function was diagnosed in the first three months after the autologous procedure while the patient remained in major molecular response on imatinib. Cytopenias worsened and additional cytogenetic abnormalities were identified with a myelodysplasia international prognostic score (IPSS) reaching 1.5 in July 2014.
specific antibodies directed against the paternal antigens were still present.

Results

Neutrophil recovery (> 1G/l) occurred on D + 16 without any platelet recovery. Daily platelet transfusions were needed to maintain platelet count above 50 G/l to reduce the risk of hemorrhagic cystitis. We also used etrombopagolamine 50 mg once a day, a thrombopoetin receptor activator, without any significant efficacy. A normal marrow activity with no sign of myelodysplasia and 100 % donor marrow chimera is documented on D + 55 and no Bcr-Abl transcripts were identified in the marrow and the blood by real-time quantitative polymerase chain reaction.

The previously diagnosed hemorrhagic cystitis reactivated with a high BK virus proliferation in urine and blood samples on D + 4 (9.98 log BK virus in blood) and the patient suffered from severe bladder bleeding with obstructive clots and acute renal failure. One injection of cidofovir on D + 6 was inefficient and surgical treatment with bilateral nephrostomies, continuous bladder irrigation and cystoscopic bladder washes were performed. Two sessions of hemodialysis were realized on D + 11 and D + 20. Injection of XIII factor (2500 UI IV) on D + 34 and intravesical cidofovir 5 mg/kg on D + 59 allowed the restoration of a normal renal function and a dramatic decrease in urinary bleedings. CsA was suspected to induce a reversible encephalopathy and immunosuppression was switched to everolimus, steroids and MMF was maintained. A Grade II digestive acute GvHD occurred on D + 45 and was treated with increased doses of corticosteroids (up to 2mg/kg) and with olimumab injections (0.3 mg/kg a day from D + 56 to D + 63 and 0.4 mg/kg 3 per week from D + 64 to D + 77) [5]. A profound persistent immunosuppression was documented on D + 100 with CD8 + T-cell, CD4 + T-cell, CD56 + NK cell and CD19 + B-cell counts above 30/ mm³.

The patient progressively developed neurologic signs of encephalopathy with temporal and spatial disorientation on D + 90. Cerebral scanner, cerebral magnetic resonance imaging and electroencephalogram were negative. Lumbar puncture identified 17,000 copies/ml of BK virus. Supplemental injections of IV cidofovir and reduction of immunosuppression did not improve the neurological symptoms. On D + 145, a sepsis with Stenotrophomonas maltophilia and Enterococcus faecium with progressive multiple organ failure was documented and the patient died on D + 161 after the second transplant.

Conclusion

Reduced intensity conditioned related haploidentical stem cell transplantation has shown efficacy and reduced toxicity in advanced Hodgkin’s lymphoma [6] and some studies also found efficacy in CML especially in accelerated phase and blast crisis [7]. In our case second allogenic graft with the use of post-transplantation Cy was particularly toxic on urine tract in a context of massive BKv-proliferation. This report is the first observation demonstrating the rapid feasibility (related donor) and efficacy despite large HLA–immunization of an emergency haploidentical stem cell transplantation after failure of reduced intensity conditioned unrelated double cord blood unit transplantation. We observed rapid hematological recovery and sustained engraftment. However immune recovery is completely deficient as previously described in patients exposed to major infectious complications in the first month post-graft particularly if increased immunosuppression is needed to control GvHD [9]. The rapid sequence with a short interval between both transplants also explains the cumulative toxicity with a fatal multiple organ failure observed in this case.

References