Treatment of severe life-threatening graft-versus-host disease by autologous peripheral blood stem cell transplantation using a non-myeloablative preconditioning regimen

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Graft-versus-host disease (GVHD) is the major obstacle to successful allogeneic stem cell transplantation (SCT). Although novel immunosuppressants, including tacrolimus (FK506), have been introduced clinically, the probability of grade II-IV acute GVHD is still relatively high, at 32-33 % in related SCT[1, 2] and 34-56 % in unrelated SCT.[3, 4] Furthermore, a significant proportion of patients prove refractory to all treatments for GVHD. On the other hand, clinical trials have shown early remission of refractory autoimmune disorders after autologous or allogeneic SCT.5 GVHD is considered to be a pathological state caused by abnormally activated donor lymphocytes. Therefore, re-transplantation with cryopreserved host-derived hematopoietic stem cells may improve refractory GVHD by destroying the abnormal lymphocytes. We report here a case of successful control of refractory, life-threatening GVHD using autologous peripheral blood stem cell transplantation (autoPBSCT).

In December 2000, a 38-year old man was diagnosed as having acute myeloid leukemia (FAB-M5b), and underwent autoPBSCT in May 2001 in the first complete remission (CR). However, the patient had hematologic relapse 6 months after autoPBSCT. After receiving salvage chemotherapy, the patient achieved a second CR, and was transferred to our hospital to undergo allogeneic SCT, because the second CR was not considered likely to be permanent. He had no HLA-identical related or unrelated donors. He had no siblings, and his parents were too old and his child was too small to donate bone marrow (BM). Therefore, we decided to perform allogeneic SCT from his HLA-2-antigen-mismatched cousin. Institutional review board approval was obtained for the treatment protocol, and written informed consent was obtained from the patient and the donor.

The transplant procedure was performed as previously described.[6] The conditioning regimen consisted of fludarabine 30 mg/m^2 days –10 to –7, cyclophosphamide 60 mg/kg on days –5 to –4, and fractionated total body irradiation (10 Gy in four fractions on days –3 and -2). GVHD prophylaxis consisted of continuous intravenous infusion of FK506 0.03 mg/kg/day from day –2, methotrexate 10 mg/m^2 on day 1 and 7 mg/m^2 on day 3, methylprednisolone (mPSL) 2 mg/kg from day 1, and oral mycophenolate mofetil (MMF) 15 mg/kg/day daily from day 5. The patient received marrow without any manipulation. Hematopoietic reconstitution was rapid, with absolute neutrophil count >0.5x10^9/L on day 11, and platelet count >20x10^9/L on day 18. However, the patient began to develop diarrhea and skin rash on days 19 and 24, respectively, while receiving a relatively high dose of mPSL (1.7 mg/kg/day) (Figure 1). The diagnosis of GVHD (grade III) was pathologically confirmed by examining the skin biopsy specimen. Although the patient was given antithymocyte globulin (ATG) and methotrexate in addition to an increase in the MMF dose, the GVHD could not be well controlled. Since the level of expression of the WT1 gene, one of minimal residual disease markers of leukemia, in the PBSC that had been harvested during the first CR was relatively low (1.4x10^{-4}),[7] we decided to perform re-transplantation in the patient using autologous PBSC. Written informed consent was obtained from the patient and his family.

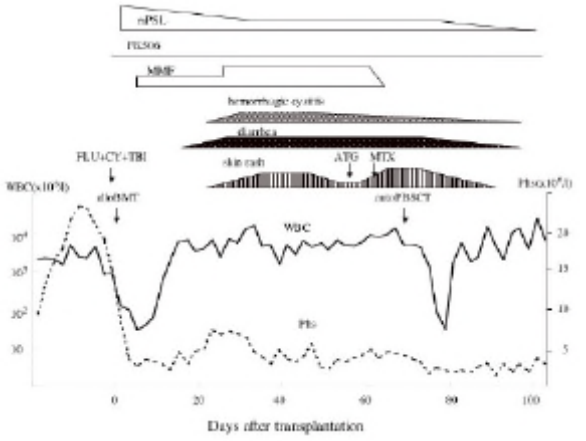

Figure 1. Clinical course of the patient. The patient received autologous transplantation 70 days after allogeneic transplantation using peripheral blood stem cells that were cryopreserved during his first complete remission. mPSL, methylprednisolone; FK506, tacrolimus; MMF, mycophenolate mofetil; FLU, fludarabine; CY, cyclophosphamide; TBI, total body irradiation; alloBMT, allogeneic bone marrow transplantation; ATG, antithymocyte globulin; MTX, methotrexate.

The conditioning regimen consisted of ATG (Lymphoglobulin, IMTIX-SangStat, Lyon, France) 2 mg/kg on days -5 to -2, thiotepa 10 mg/kg on day –2 and TBI 2 Gy on day 0. The patient received autoPBSC containing 14.1x10^6 CD34 cells/kg on day 70 after allogeneic SCT. Absolute neutrophil counts greater than 0.5x10^9/L were achieved on day 10 after the second autoPBSCT. A donor/recipient chimerism analysis of peripheral blood on day 10 using short tandem repeat polymerase chain reaction showed 100 % recipient (patient) T-cell and granulocyte chimerism. The symptoms and signs of GVHD began to improve 2 weeks after the second autoPBSCT and had largely resolved on day 30 (Figure 1). However, the patient had a marrow relapse on day 144 after the second autoPBSCT.

We showed that refractory GVHD could be controlled by autoPBSCT. As far as we know, there have been two reports (three patients) about autologous hematopietic stem cell transplantation to treat refractory GVHD.[8, 9] The symptoms of GVHD in all the patients resolved following the autologous transplant procedure. In most cases of severe GVHD, since patients have organ damage caused by GVHD, a non-myeloablative conditioning regimen is preferred in order to decrease regimen-related toxicity. Although relapse was a problem with this treatment in the present case, as also reported by others,9 the reversal of life-threatening GVHD will make it possible to perform some treatment procedures to prevent relapse.

In conclusion, autologous transplantation using non-myeloablative preconditioning is one of the modalities for treating refractory GVHD.

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