Successful Allogeneic Stem Cell Transplantation with Fludarabine-based Conditioning Regimen in Severe Aplastic Anemia

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Abstract
Graft failure is a problem in HLA-identical sibling transplants for patients with refractory severe aplastic anaemia (SAA). Intensification efforts includes addition of radiation or biologic agents such as antithymocyte globulin (ATG), procarbazine or cyclophosphamide has often been advocated to combat this problem. With this approach engraftment rate has improved. However the incidence of transplant related complications are also increased, resulting in little change in the overall outcome. We therefore investigated the use of combination of fludarabine and cyclophosphamide as a non-myeloablative conditioning regimen in a patient who was refractory to multiple immunosuppressive agents and transfusions. He received peripheral blood stem cells from his HLA-identical sibling donor. With a follow up of eighteen months, the patient is alive with complete and durable hematopoietic engraftment. Fludarabine-based conditioning regimen therefore has the potential to be successfully and safely used in patients with SAA undergoing transplant.

**INTRODUCTION**

Fludarabine-based conditioning has been reported to facilitate allogeneic marrow engraftment with tolerable side effects. Most of this data involved patients with underlying malignancies.1 We report a case of SAA who successfully received allogeneic peripheral blood stem cell transplant (PBSCT) following non-myeloablative conditioning regimen with fludarabine and cyclophosphamide.

**CASE REPORT**

A 37 years old male presented with hematuria and low grade fever in September 1999. There was no family history of hematological disorder. The diagnosis of hypoplastic anemia was based on WBC of 3.52x10⁹/l, ANC-1.11X10⁹/l, Hb-8.4G/dl, Platelet count of 15x10⁹/l, reticulocyte count of 3% and bone marrow biopsy revealing hypoplastic anemia. Investigations for paroxysmal nocturnal hemoglobinuria (PNH) being negative. The patient was treated with cyclosporine A (CSA) and anti-thymocyte globulin (ATG) with poor response. Subsequently CBC revealed WBC -1.2 x 10⁹/l, ANC -0.845x10⁹/l, Hb 8.4 G/dl, platelet count 15x10⁹/l. He was then given high dose of cyclophosphamide 45 mg/kg for 4 days. He continued to remain pancytopenic with Hb 8.01 G/dl, WBC 1.48 x 10⁹/l, ANC - 0.476 x 10⁹/l, Platelet count 9.43 x 10⁹/l six months after this second line treatment. During this period, he received 55 transfusions of blood products. At this point allogeneic stem cell transplant was planned. The donor was his HLA identical sibling brother. There was a minor ABO mismatch. Investigations done prior to PBSCT showed Hb - 8.83% G/dl, WBC - 2.21X10⁹/l, ANC - 0.738X10⁹/l, Platelet count - 11.9X10⁹/l and reticulocyte count 0.2%. He received conditioning with fludarabine (30 mg/m²/day IV from D-8 to D-4) and cyclophosphamide (30 mg/kg/day from D-3 to D-2). The peripheral blood stem cell (PBSC) harvest showed mononuclear cells (MNC) of 5.03 x 10⁹/kg and CD34 positive cells of 2.27x10⁹/kg body weight. On day 0, the patient received these G-CSF mobilised PBSC without any in vitro manipulation. He was given GM-CSF 5 µg/kg iv infusion from Day 1 onwards to hasten hematopoietic recovery. GVHD prophylaxis consisted of CSA 3 mg/kg daily IV was given on D-1 to Day +120 and methotrexate 8 mg/m² IV was given on day +1,+3,+6 and +11 posttransplant. He received routine gut prophylaxis and CMV prophylaxis. The post-transplant period was complicated by febrile neutropenia on Day +3 which was managed with antibiotics and resolved on day +16. Acute GVHD was grade II and was successfully treated by methyl-prednisolone 2 mg/kg/day. It resolved by day +24. He showed a hematological recovery in the myeloid lineage with the achievement of ANC > 0.5 x 10⁹/l by day +13 and unsupported platelet > 20,000/µl by day +55. He developed

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chronic skin GVHD on Day +162 (proved by skin biopsy) for which a combination of oral prednisolone, CSA and mycophenolate mofetil was given. This was continued till day +356. At the time of reporting, he has completed 16 months posttransplant, is off immunosuppressive drugs and is transfusion-independent. He is alive with KPS of 100%. His Hb is 15.1 G/dl, WBC - 6.41X10⁹/l, ANC - 3.18X10⁹/l and Platelet count - 113 x 10⁹/l. Bone marrow biopsy confirms recovery of normal hematopoiesis and cellularity.

**DISCUSSION**

Allogeneic hematopoietic stem cell transplant (HSCT) is a potentially curative treatment for patients with SAA. However complications contribute significantly to morbidity and mortality. Patients are often multiply transfused with resultant allosensitization to minor histocompatibility antigens. Pretransplant profound neutropenia of long duration predisposes to repeated infections and poor general condition.

Intensification of the cyclophosphamide-based preparative regimen by addition of irradiation, either as limited field or total body irradiation (TBI) has been advocated to minimize graft rejection. However the outcome of irradiation-based bone marrow transplant has been variable. Patients who had received irradiation had a higher incidence of GVHD and interstitial pneumonitis.² In addition the incidence of second malignancies is often high, in patients who received irradiation. Avoidance of radiation in the preparative regimen is therefore desirable, provided we find another way to reduce graft rejection.

Use of cyclophosphamide and ATG has resulted in conflicting outcome.³⁴

Purine analogues especially, fludarabine posses powerful immunosuppressive action. Fludarabine-based preparative regimen were sufficient to lead to successful engraftment in patients with hematologic malignancies using either matched sibling or alternative donors.³

Therefore fludarabine would be an attractive agent to be incorporated into a HSCT conditioning regimen even for patients with SAA. On the other hand, the ability to reject a transplant remains of concern for several reasons. The immune system of patients with SAA may be more intact than that of leukemia or lymphoma patients, who have had prior anticancer therapy. Frequent transfusion of blood products in SAA patients could have also enhanced the allogeneic resistance to donor grafts.

Chan et al treated five patients of SAA with fludarabine-based conditioning regimen in heavily transfused patients.⁶ They did not develop significant toxicity. These patients did not have an HLA matched donor. Yet, one of them had sustained donor engraftment for over six months and could also be off GVHD prophylaxis. Our patient was heavily transfused prior to HSCT. It is therefore reassuring that he engrafted despite the unfavorable prognostic factors. He has engrafted since over 17 months. We therefore conclude that, fludarabine-based conditioning has the potential to be safely and successfully used in patients with SAA undergoing HSCT.

**REFERENCES**