Two allogeneic hematopoietic stem cell transplantations without the use of blood-product support

We successfully performed two allogeneic hematopoietic stem cell transplantations from matched unrelated donors without the use of blood-product support after treosulfan-based conditioning in two women with acute myeloid leukemia who were Jehovah's witnesses and refused transfusions of blood products.

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In the last two years we were confronted with a mother and her daughter with acute myelogenous leukemia (AML) who were both members of the community of Jehovah`s witnesses, a religious group that refuses transfusion of any major blood product.

Despite their religious objection to blood products we offered both induction chemotherapy and allogeneic hematopoietic stem cell transplantation as consolidation therapy, which they accepted. We felt able to propose this strategy for two reasons: (i) based on our experience with a stringent therapeutic platelet transfusion protocol that we have developed during the last years, we know that severe thrombocytopenia can be managed without prophylactic platelet transfusion. In more than 200 patients (during induction chemotherapy for AML or after autologous peripheral stem cell transplantation) we have shown that a therapeutic transfusion strategy is safe.

In one third of our patients autologous transplantation could be performed without any platelet transfusions. Bleeding complications among patients transfused on demand were completely comparable to those among our former patients who received prohylactic platelet transfusions at a trigger platelet count of 10×10^9/L;[1,2] (ii) we used allogeneic stem cell transplantation after a reduced toxicity conditioning regimen as consolidation treatment since hematologic regeneration could be expected to be significantly quicker than after repeated cycles of high-dose cytosine arabinoside as consolidation. The same is true for autologous transplantation because stem cells should be collected only after a minimum of two intensive courses of chemotherapy as *in vivo* purging. The risks of graft-versus-host disease (GVHD) after allogeneic transplantation and its higher probability of cure had to be weighed against the greater hematologic and non-hematologic toxicity of the alternative procedures.

In the daughter we favored allogeneic transplantation despite normal cytogenetics because her AML was diagnosed as a first relapse after a chemotherapy-treated AML as a child more than 10 years previously. The mother was informed that allogeneic transplantation from a matched unrelated donor is not standard therapy in AML in first remission without high-risk cytogenetics. Both patients were informed on the extraordinary risks of refusing blood transfusions during the treatment of AML. Both patients gave their written informed consent.

Table 1. Patients' characteristics and follow-up.

	Mother	*Daughter*
Diagnosis	AML-M1	AML-M2
Karyotype	Normal female	Normal female
Status of remission before transplantation	CR	CR
Age at transplantation	48	21
Conditioning regimen	TBI/Fludarabine/Treosulfan	TBI/Fludarabine/Treosulfan
Donor	Matched unrelated male	Matched unrelated male
Blood group P/D	A Rh+/A Rh+	A Rh+/A Rh+
CMV	P^-/D^-	P^-/D^-
Source of stem cells	Bone marrow	Peripheral blood
No. of transplanted cells ($CD34\times10^6$/kg)	1. 64	8.4
Immunosuppression (oral)	CSA/MMF(4×500mg)	CSA/MMF(4×500mg)
Hematologic toxicity		
Leukocytes <1.0×10^9/L (days)	6	14
Neutrophils <0.5×10^9/L (days)	12	18
Platelets <20×10^9/L[<10×10^9/L]	2 [0]	3 [0]
Minimal hemoglobin (g/dL)	11	9
Chimerism analysis (FISH)	> 90% donor, day +15, ongoing	> 90% donor, day +12, ongoing

TBI: total body irradiation; P: patient; D: donor; CSA: cyclosporine A; MMF: mycophenolatmofetil; FISH: fluorescent in situ hybridization.

The characteristics of the patients, their treatment and the follow-up are shown in Table 1. A complete remission was achieved after dose-reduced induction chemotherapy with daunorubicin (50 mg/m^2×2) and cytosine arabinoside (100 mg/m^2 for 5 days as a continuous infusion). Once HLA-identical unrelated donors had been identified for each patient we started conditioning in both with a combination of a marrow ablative dose of treosulfan (3×10 g/m^2) and fludarabine (5×30 mg/m^2) in combination with 4 Gy total body irradiation.

Treosulfan (L-threitol-1,4-bis-methanesulfonate; dihydroxybusulfan; NSC 39069) is a prodrug of a bifunctional alkylating cytotoxic agent that is approved for the treatment of ovarian carcinoma in a number of European countries. Beside its potent hematopoietic stem cell toxicity, treosulfan has also demonstrated *in vitro* activity against a variety of hematologic malignancies including acute leukemias.[3,4] In a recently published phase II study on patients not eligible for conventional conditioning, this drug was associated with a very low non-hematologic toxicity.[5] Mucosal toxicity was minimal and the duration of leukocytopenia and thrombocytopenia was short because leukocyte and platelet counts decline very slowly after high-dose treosulfan. Unlike Casper *et al.*[5] we did not use rabbit antithymocyte globulin (ATG) in the conditioning regimen because of the increased risk of bleeding associated with decreasing platelet counts during infusion of ATG. For additional immunosuppression ATG was replaced with 4 Gy total body irradiation. As GVHD prophylaxis both patients received a combination of cyclosporine and mycophenolate mofetil. Hematopoietic growth factors (granulocyte colony-stimulating factor and darbepoetin) were given during the transplantation phase in the mother because she received bone marrow. Peripheral blood stem cells were our first choice for transplantation because of the quicker hematologic regeneration following transplantation of stem cells from this source. However, the donor for the mother preferred donating bone marrow. Before transplantation the patients' hemoglobin levels were 12.8 and 12.2 g/dL and platelet counts were within the normal range.

Neither patients developed severe thrombocytopenia (<10×10^9/L). The duration of thrombocytopenia (< 20×10^9/L) was 2 and 3 days, the duration of leukocytopenia (< 1.0×10^9/L) was 6 and 14 days and the lowest hemoglobin level was 11.2 and 9.1 g/dL in the mother and daugther, respectively. Full donor chimerism was achieved in both patients within three weeks. In the mother follow-up was complicated by mild GVHD of the gastrointestinal tract, promptly controlled by steroids, and long-lasting anemia necessitating erythropoetin support for 3 months. The early use of erythropoetin in the case of anemia and close monitoring of iron and ferritin levels in the blood are recommended in these patients who refuse blood transfusions for religious reasons. The daughter experienced no non-hematologic toxicity and maximal grade II GVHD of the skin and gastrointestinal tract. The mother and daughter remain in complete hematologic remission 20 and 12 months after their respective transplants.

We conclude that this intensive treosulfan-based preparative regimen for allogeneic transplantation has low hematologic and non-hematologic toxicity despite its myeloablative potential. This conditioning regimen may be especially suitable in clinical situations in which a non-myeloablative mini-transplant may place patients at an increased risk of early disease recurrence because of the proliferative activity of the underlying hematologic malignancy.[6] Even Jehovah`s Witnesses who are not intensively pretreated can be transplanted successfully following this myeloablative conditioning regimen. Our experience parallels a recent report from Ballen *et al.*[7] on 26 Jehovah's Witnesses who successfully underwent autologous transplantation of peripheral blood stem cells without any blood product support.

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