Report

Bone marrow transplantation in thalassaemia patients in Shiraz, Islamic Republic of Iran

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SUMMARY We report the results of allogeneic bone marrow transplantation in 26 female and 37 male patients with β-thalassaemia major (age range: 2–17 years), performed at Namazi Hospital over the period 1992–99. In all cases, standard conditioning and immunosuppressive regimens were employed. Currently, 50 patients remain thalassaemia-free, 9 of whom have developed chronic graft-versus-host disease. There were 8 deaths among the 13 unsuccessful transplant cases: 4 due to acute uncontrollable graft-versus-host disease, and 4 to non-transplant-related causes such as hypoglycaemia, hypersensitivity reactions and advanced disease. We conclude that allogeneic bone marrow transplantation is an effective therapy for the treatment of β-thalassaemia major, particularly for patients classified as classes I and II.

Introduction

In the clinical management of thalassaemia, advances in the past two decades, such as regular blood transfusion combined with optimal Desferal infusion, have helped to improve the quality of life of patients. Despite the improvements, however, disease outcome has remained largely unchanged, with many patients still dying in the third decade of life from iron-induced organ damage [*1*]. It is unlikely that advances in molecular biology in the near future will provide an acceptable, certain alternative mode of therapy [*2*]. Within this context — of 20 years of marrow transplantation as a salvage therapy — we present the experience of our centre at Namazi Hospital, Shiraz, Islamic Republic of Iran, during the 8-year period, 1992–99 [*3*].

Methods

Over the 8-year period, 63 patients underwent bone marrow transplantation in our centre. The patients were first prepared with conditioning chemotherapy consisting of busulfan (a total 15 mg/kg given over 4 days), cyclophosphamide (200 mg/kg, in 50 mg/kg doses over 4 days) and antithymocyte globulin (40 mg/kg). Ciclosporin (Sandimmune) was given intravenously as a prophylaxis for acute graft-versus-host disease (GVHD), commencing with 5 mg/kg from day –2 to day +6 of marrow infusion. This was followed by a daily dosage of 3 mg/kg intravenously, or 12.5 mg/kg orally, until day +60 post-marrow transplantation, and gradually tapering thereafter by 5% every 2 weeks until 1 year post-transplantation. Prednisolone (0.5 mg/kg

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per day) was given from day −1 until 3 weeks post-marrow transplantation.

During transient post-chemotherapy neutropenia, all patients were isolated in a low microbial environment with filtered air. Prophylactic antibiotics and antifungals were given to all patients until the absolute neutrophil count rose to > 500 cells/μm^3. Sandoglobulin (Sandoz) was given intravenously to all patients to prevent cytomegalovirus infection.

All blood products were irradiated with cobalt 60 (3000 rads) to prevent post-transfusion GVHD. In all cases, patient and donor were matched negatives. Diagnosis of thalassaemia was established by haemoglobin electrophoresis. Post-transplantation, reticulocyte count and haemoglobin electrophoresis were used as tests in patient follow-up [*4*]. Marrow was collected from the donor under general anaesthetic by bilateral iliac crest aspiration. The average cell dose of the marrow was 2×10^8 cell dose/kg. The marrow was infused through a peripheral intravenous line.

Results

Of the 63 patients with β-thalassaemia major undergoing transplantation during the period, 26 were female and 37 were male, with an age range of 2–17 years (average age: 11 years) (Table 1). Up to the present time, 50 successfully transplanted cases remain thalassaemia-free. Of these, 9 cases have developed chronic GVHD, which, with the exception of two patients, is controlled with immunosuppressive agents. There were five cases of rejection (Table 2). Of the 13 cases in which transplantation was unsuccessful, there were 8 deaths, 4 of which were due to acute or uncontrollable GVHD and 4 to non-transplant-related situations such as hypoglycaemia, hypersensitivity reactions and advanced disease (Table 2).

Table 1 **Characteristics of 63 thalassaemia patients undergoing bone marrow transplantation at Namazi Hospital, Shiraz, Islamic Republic of Iran, 1992–99**

Characteristic	No.
Class	
III	55
II	8
Sex	
Female	26
Male	37
Chronic GVHD	8
Overall survival (%)	75

The age range was 2–17 years (mean age 11 years).
GVHD = graft-versus-host disease.

Discussion

Because of high mortality rates associated with iron-induced organ damage, toxicity of chemotherapy regimes, infection and

Table 2 **Adverse events in 63 thalassaemia patients following bone marrow transplantation at Namazi Hospital, Shiraz, Islamic Republic of Iran, 1992–99**

Event	No.
Total deaths	8
Bacterial sepsis	2
Drug reaction	1
Hypoglycaemia	1
Acute GVHD	2
Uncontrolled GVHD	2
Rejection	5

GVHD = graft-versus-host disease.

acute GVHD [5], marrow transplantation therapy was initially considered a high-risk procedure [6]. However, experience in many centres has shown that by modulating the conditioning and immunosuppressive regimens (particularly in patients without severe, irreversible organ damage [5]), and by including new antibiotics and antifungals, marrow transplantation can be an effective therapy. Our results with 55 class III patients (i.e. those with portal fibrosis and severe iron-induced liver damage) concur with the published data of others, notably the Pesaro group in Italy [5], which has carried out bone marrow transplants on more than 800 patients. They have reported a 90% cure rate for class I patients and an 80% cure rate for class II patients (hepatomegaly or portal fibrosis). By contrast, the event-free survival rate for heavily iron-laden patients (class III) was approximately 50% [5].

At Namazi, where we carried out transplantations using a fixed conditioning regimen, our results were acceptable, and similar to those at Pesaro. Although we selected potential transplant patients using an age range of 2–17 years, age is not an independent factor for thalassaemic marrow transplantation: rather, it is the class of patient that is the more important [7]. Class I and class II patients are more suitable candidates for transplantation than class III patients because iron-induced organ damage is present to a lesser extent in the former, and so marrow transplantation is better tolerated.

Conclusion

Allogeneic marrow transplantation is an effective treatment for β-thalassaemia major. In determining the suitability of a patient for treatment, social and ethical considerations require that the patient and patient's family be fully informed of possible outcomes, as well as current morbidity and mortality rates for bone marrow transplantation.

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