Blood Reviews 28 (2014) 243–248

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Blood and marrow transplantation for sickle cell disease: Is less more?

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ARTICLE INFO

Keywords:
Sickle cell disease
Bone marrow transplant
Graft-versus-host disease
Alternative donors

ABSTRACT

Blood and marrow transplantation is a curative therapy for patients with sickle cell disease yet this option is seldom used. Clinical studies have shown however that children transplanted for this condition can achieve excellent results. In children with sickle cell disease transplanted following conditioning with busulfan, cyclophosphamide, and anti-thymocyte globulin, cure rates in excess of 80% can be obtained when an HLA-matched sibling is used as the donor. However, the large majority of patients with sickle cell disease will not have such a donor, or will not be able to tolerate high dose conditioning regimens. Therefore novel approaches such as non-myeloablative regimes, and alternative donors such as haploidentical, unrelated, or cord blood grafts are currently being explored in clinical trials. Recent reports on non-myeloablative conditioning (HLA-matched or haploidentical donors) highlight the safety and efficacy of these approaches with low mortality and high efficacy suggesting that in the near future non-myeloablation could be the preferred type of conditioning and donor availability will not be a barrier anymore to proceed to transplant. This review will focus on the results obtained when bone marrow transplants are used to treat sickle cell disease and will discuss the results obtained with these novel approaches.

1. Introduction

Sickle cell disease (SCD) kills nearly half a million people annually. In 2010 there were more than 300,000 newborns with SCD [1]. In the United States, SCD is the most common inherited blood disease affecting nearly 100,000 children and adults. The annual cost for medical care for SCD patients in the United States exceeds 1 billion dollars. For adults with SCD the average annual cost of medical care exceeds 35,000.00 US dollars per year [2]. Survival of patients with SCD has improved in developed countries due to improved supportive care, judicious use of blood transfusions, prophylactic antibiotics, and drug therapy with hydroxyurea. Despite these advancements, most adults and many children develop a chronic debilitating condition, with over 30% of adults on disability and over 50% of patients unemployed [3]. Median survival is shortened by more than two decades and quality of life is severely impacted due to complications of chronic pain, narcotic dependence, stroke, renal failure, thrombosis, pulmonary hypertension, blindness, priapism, and infection.

Allogeneic blood and marrow transplantation (BMT) can cure SCD; however, BMT is seldom used for these patients due to perceived toxicity and lack of suitable donors. As of 2013, there were 1238 BMTs for SCD reported to the CIBMTR and EBMT-Eurocord [4]. In 1984, Johnson et al., reported a successful BMT of a child with leukemia and SCD who was cured of both disorders [5]. This was followed by several reports of myeloablative allogeneic BMT from matched sibling donors for children in SCD [6,7]. These data firmly established that SCD is a potentially curative disease following myeloablative allogeneic BMT from a healthy HLA matched sibling donor. Unfortunately, BMT is available only in developed countries. Even in these countries, there are numerous obstacles such as donor availability, transplant related morbidity and mortality, and engraftment difficulty in patients with SCD, that limit the availability of BMT to only a small percentage of patients [8,9]. The past decade has witnessed dramatic progress in improving safety and expanding the donor pool for patients in need of BMT. This review will focus on the indications, the outcomes, and recent advances for expanding the donor pool for patients with SCD.

2. Indications for BMT

Indications for BMT in patients with SCD continue to evolve and clearly there is no consensus about these (Table 1) [10]. The majority of the published series report on highly symptomatic SCD with advanced disease [7,8,11,12]. Until recently, virtually all BMTs in SCD was performed in children using myeloablative conditioning and matched related sibling donors. This meant that parents of patients with SCD were often put in the difficult position of making the final decision. Now that non-myeloablative conditioning regimens and HLA-

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http://dx.doi.org/10.1016/j.blre.2014.08.001
0268-960X/

Table 1
Common indications to proceed with BMT.

Indications for BMT	
Commonly accepted	Stroke/cerebral ischemia
Frequently accepted	Recurrent acute chest syndrome
	Frequent vaso-occussive/pain crises
	Red cell alloimmunization
	Osteonecrosis

haploidentical donors are showing success in children and adults with SCD, the indications continue to evolve and adult patients are now able to sign consent forms [9,13]. Most pediatric hematologist agree that stroke or silent cerebral infarction is an absolute indication for children with SCD, especially given recent data showing that red cell exchange transfusions are not as effective as previously thought in preventing secondary vascular events [14]. Recurrent acute chest syndrome or frequent vaso-occlusive crisis despite hydroxyurea with good compliance is also considered to be a good indication for BMT in children. Others feel that all symptomatic children with SCD be transplanted as soon as possible if they have a fully matched HLA-sibling donor. In adult patients common indications have included cerebrovascular disease, recurrent vaso-occlusive crisis despite hydroxyurea, osteonecrosis, red cell alloimmunization, and recurrent acute chest syndrome [9,13]. While pulmonary hypertension is a known cause for morbidity and mortality in these patients, there is no agreement on whether it should be used as an indication to proceed to transplant and at least in one study these patients were excluded [13]. The indications for BMT in children and adults with SCD will continue to evolve as the availability of alternative donors, engraftment rates, and safety of BMT increases. Some degree of renal dysfunction should not be seen as a reason to avoid transplant (given the use of nephrotoxic drugs such as calcineurin inhibitors or fludarabine), however, data on patients transplanted for this indication on renal replacement therapy is very limited [15].

3. Patient and family perspectives

Regardless, all patients and families of patients with symptomatic SCD should be educated about the potential risks and benefits of BMT at an early age since BMT is the only proven cure for SCD. At the same time, physicians may not be aware of the perceptions that SCD patient have of BMT. Chakrabarti and Bareford surveyed thirty adult patients with SCD about their feelings towards receiving a reduced intensity BMT for the management of their disease [16]. Sixty-two percent were willing to accept a ten-percent transplant related mortality and a third of patients even a thirty-percent transplant related mortality. Most patients, 62%, were willing to accept a 10% risk of graft failure, 50% were willing to accept infertility, but only 20% considered chronic graft-versus-host disease acceptable. In fact, 60% of those surveyed would consider joining a clinical trial of reduced intensity BMT. These authors conclude that SCD patients are willing to consider the option of BMT despite the morbidity and mortality associated with the procedure.

4. High dose chemotherapy in sickle cell disease: early experiences

Historically, myeloablative conditioning regimens have been used to condition SCD patients for BMT (see Tables 2 and 3). In 1993, Bernaudin et al. published their results on 15 children with severe SCD transplanted with bone marrow from HLA identical siblings [6]. At BMT, mean age was 8 years and 7 months. Donors were hemoglobin AS (n = 11) or AA (n = 4). Conditioning regimens employed busulfan and cyclophosphamide with or without anti-thymocyte globulin (ATG) or total lymphocyte irradiation. Graft-versus-host disease prophylaxis included cyclosporine and metothrexate. Median follow-up was 28 months. Ten patients engrafted with stable complete donor chimerism; 4 patients had mixed chimerism.

In 1996, Walters et al. published a series of 22 children with SCD conditioned with ATG (or alemtuzumab), cyclophosphamide and busulfan and transplanted bone marrow grafts from HLA-identical donors [7]. All patients were younger than sixteen and had "advanced" disease (history of stroke, recurrent acute chest syndrome, abnormal brain imaging, retinopathy, bone disease, etc.). With a median follow-up of two years 90% of the patients survived and 72% had stable chimerism. The graft-rejection rate was low (13%). Neurologic events were relatively common and included seizures and stroke as well as 2 deaths due to stroke.

Vermylen et al. reported on fifty pediatric patients with SCD transplanted (48 bone marrow and 2 cord blood) in Europe [17]. Overall survival was over 90% at eleven years. Acute graft-versus-host disease was present in twenty patients and one patient developed acute myeloid leukemia. Of these 50 patients, 36 had severe disease that met consensus criteria for BMT; 14 had less severe disease and were transplanted because they decided to return to their country of origin. In the 36 patients with more severe SCD overall survival, event-free survival and disease-free survival at 11 years was 88, 76 and 80%, respectively. Outcomes were slightly better for the less symptomatic and less transfused cohort of 14 patients. Gonadal dysfunction was present in all patients transplanted close to or after puberty.

In 2000, Walters et al. published a study on another group of fifty patients with symptomatic SCD transplanted between 1991 and 1999 [11]. Again all were young (less than fourteen years of age). Overall

Table 2
Results of selected BMT reports using different strategies for allogeneic transplantation in patients with sickle cell disease: myeloablation and non-myeloablation.

	Myeloablative matched				Non-myeloablative matched
	Walters [11]	Vermylen [17]	Bernaudin [12]	Panepinto [18]	Hsieh et al.[9]
Number of patients	26	50	87	67	30
OS	94%	96%	96%	96%	96%
EFS	84%	82%	91%	85%	87%
TRM	6%	7%	7%[a]	0	0
Graft failure	10%	10%	7%	13%	13%[b]
Ages	3–15	1–23	2–22	2–27	17–65
Acute GvHD	3	20	17	8	0
Chronic GvHD	2	10	11	13	0

OS: overall survival; EFS: event-free survival; TRM: transplant related mortality; GvHD: graft-versus-host disease.
[a] Estimated at 5 years.
[b] 3 patients required a second BMT, 2 engrafted after the second.