Transfusion and Apheresis Science 49 (2013) 151–154

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

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

Sickle cell anaemia: Current therapies

Christiane Vermylen *

Department of Paediatric Haematology and Oncology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium

A B S T R A C T

Tremendous progress has been made in the treatment of patients with sickle cell anaemia. This paper emphasises the benefit of early therapy with hydroxyurea, the indication for blood transfusions including iron chelation and the role of hematopoietic stem cell transplantation. In order to offer transplantation to a larger number of patients including adolescents and young adults, it is important to find less toxic, but still effective conditioning therapy and to evaluate the feasability of using alternative donors.

Contents

1. Introduction

Sickle cell anaemia is characterised by haemolysis and vasoocclusive phenomena with recurrent painful episodes that can lead to life-long disabilities and death.The management of sickle cell anaemia includes the prevention of complications by penicillin prophylaxis since the newborn period, appropriate immunisations and blood transfusions for patients at risk for stroke. Hydroxyurea is the only FDA approved therapy to prevent pain episodes and anaemia. Based on the BABY HUG trial, infants with more severe anaemia are at risk for increased clinical events that may be prevented by early initiation of hydroxyurea [1]. Hydroxyurea can now be considered for very young children with sickle cell anaemia [2].

A high risk of stroke is observed in children with sickle cell anaemia and abnormal transcranial Doppler (TCD) ultrasonography. This risk is greatly reduced when chronic transfusion therapy is administered [3]. So far, haematopoietic stem cell transplantation (HSCT) is the only therapy able to offer a cure for sickle cell anaemia [4].

Thanks to the prophylactic measures, infants and young children are surviving much longer than before. However, there is a disturbing increase in mortality of older children and adults that may reflect inadequate preventive measures for acute chest syndrome and organ failure [5].

* Tel.: +32 2 764 1300; fax: +32 2 764 8964.
E-mail address: christiane.vermylen@uclouvain.be

1473-0502/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.transci.2013.07.018

2. The BABY HUG trial

This randomized trial was undertaken in 13 centres in the USA between October 2003 and September 2009. Children with sickle cell anaemia were aged 9–18 months at randomisation. Ninety six children received liquid hydroxycarbamide (20 mg/kg per day) and 97 received placebo for 2 years. Splenic and renal functions were chosen as primary endpoints because dysfunction occurs early in life.

A lot of information was drawn from this trial. In general, infants with lower haemoglobin at baseline were more likely to have a higher incidence of clinical events (acute chest syndrome, pain crises, fever) as well as higher TCD velocities and lower neuropsychological scores at study exit [1]. Loss of splenic function began before 12 months of age in 86% of infants in association with lower total or fetal haemoglobin and higher white blood cell or reticulocyte counts. Hydroxycarbamide significantly decreased pain and dactylitis, with some evidence for decreased acute chest syndrome, hospitalisation rates and transfusion. Hydroxycarbamide increased haemoglobin and fetal haemoglobin and decreased white blood-cell count [2]. Measures of splenic function (Howell-Jolly bodies, pit counts and ratio of spleen to liver count) suggested benefit from hydroxycarbamide [2,6]. However ultrasonographic spleen volume did not reflect function [7]. Higher urine osmolality and specific gravity suggested benefit from hydroxycarbamide as far as the kidney function was concerned [8]. A greater total kidney volume on ultrasonography in the placebo group might indicate nephromegaly due to hyperfiltration [7]. In addition, the trial showed that the average increase in TCD velocity was significantly less in those receiving hydroxycarbamide than in those receiving placebo. Toxicity was limited to mild-to-moderate neutropenia [2]. Further follow-up of the BABY HUG cohort is now planned until 2016, when participants will be 9–13 years of age, and will provide data for longer-term beneficial and toxic effects.

The conclusion of the study was that hydroxycarbamide can now be considered for very young children with sickle cell anaemia.

3. Blood transfusions

Stroke occurs in about 11 percent of patients with sickle cell anaemia by the age of 20. Blood transfusions prevent recurrence of stroke. Prevention of a first stroke in children with abnormal results on TCD ultrasonography was demonstrated in the Stroke Prevention trial in Sickle Cell Anaemia (STOP). This trial showed that regular red cell transfusions administered to maintain the haemoglobin S level below 30% of total haemoglobin reduced the risk of stroke in those with abnormal TCD by more than 90% [3]. Predictors of developing a normal TCD were analysed. Younger children with higher pre-transfusion haemoglobin levels and lower abnormal TCD velocities were most likely to have rapid normalisation of TCD on transfusions [9]. STOP 2 was a follow-up study to STOP, designed to assess whether transfusion therapy could be safely halted after at least 30 months of adequate transfusion therapy in those who reverted from abnormal to normal TCD. The study was stopped earlier than planned because discontinuation of transfusion for prevention of stroke resulted in a high rate of reversion to abnormal velocities on Doppler and stroke [10]. Chronic transfusions reduce recurrent strokes but have associated morbidities including iron overload. The Stroke With Transfusions Changing to Hydroxyurea (SWITCH) trial compared standard transfusions and chelations with hydroxyurea and phlebotomy. None of the 66 patients on the standard treatment but 7/67 on the hydroxyurea arm developed strokes. Transfusions and chelation therapy remain a better way to manage children with sickle cell anaemia, stroke and iron overload. The potential neurologic benefits of hydroxyurea therapy early in life are currently under investigation in the BABY HUG follow-up studies and one may hope that early initiation of hydroxyurea will help prevent cerebrovascular disease [11].

4. Hematopoietic stem cell transplantation

Allo HSCT is the only curative strategy for patients with sickle cell anaemia. Since 1984, traditional myeloablative conditioning regimens were used in Europe and in the Unites States. Based on 5 major studies, overall survival of 92–94% and event-free survival of 82–86% were reported [12]. One series reported that transplantation may be performed more safely in younger paediatric patients who had not experienced end-organ damage [13]. On the opposite, many adults with sickle cell anaemia have accumulated end-organ damage and presumed toxicity from myeloablative conditioning regimens has prohibited this potentially curative approach [4].

For young adults, the classic myeloabalative regimen might still have a place as shown by the French experience in 15 patients older than 16 years of age who have received geno-identical HSCT [14]. For older adults with organ failure, innovative nonmyeloablative protocols are crucial. The conditioning regimen should be tailored, especially that there is evidence that mixed donor chimerism can revert the disorder. Ianonne et al used 200 cGy of TBI, fludarabine and immunosuppression with cyclosporine. Patients had temporary engraftment. However, when cyclosporine was tapered, donor grafts decreased to undetectable levels [15]. Hsieh et al proposed a regimen on the basis of 300 cGy of TBI with alemtuzumab for GVHD prophylaxis and long-term administration of sirolimus (6–12 months). Alemtuzumab was chosen for better infusional toxicity profile as compared with antithymocyte globulin and superior prophylaxis against GVHD. Alemtuzumab remains detectable for several weeks after infusion and further deletes alloreactive T cells during donor engraftment and initial immune reconstitution. They further hypothesised that sirolimus coud induce sufficient number of regulatory T cells to promote tolerance in a mixed chimeric setting and reduce delayed GVHD. Ten out of 10 patients were alive and all but one had long-term donor engraftment. No patient experienced acute or chronic GVHD (14). Limitation to HSCT in sickle cell anaemia has been the absence of HLA-matched sibling donors. The use of alternative do-