

Scientific Commentaries

Hematopoietic stem cell transplant in acute leukemias in children and adolescents

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The prognosis for children and adolescents with acute leukemia has greatly improved in recent decades and is a great example of how much can be achieved through collaborative studies and multicenter clinical protocols.

Some of the elements with the greatest impact on achieving high rates of cure are: education of the medical community to diagnose cancer early; the better biological characterization of leukemia by immunophenotyping and classical and molecular cytogenetic tests; rigorous chemotherapy protocols; early and systematic evaluation of chemotherapy response; and adequate supportive treatment. Nevertheless, at least 30% of these children are still not cured by conventional treatment and may be eligible for hematopoietic stem cell transplantation.

Transplants have two major components: myeloablative conditioning regimen (chemotherapy + total body radiation) and transfusion of immunologically active cells from a healthy donor that are capable of providing an effect against leukemia.⁽¹⁾

Our goal as onco-paediatric hematologists is to heal as many children as possible, minimizing their suffering including the short- and long-term deleterious effects. All studies show that allogeneic transplants provide the best chance of remission, but the possibility of toxicity and mortality associated with the procedure should always be taken into account.

The Center for International Blood & Marrow Transplant Research (CIBMTR), for several decades, has been collecting data on all transplants performed in over 500 centers in 54 countries, including Brazil. The annual results are a valuable source for reference and consultation.⁽²⁾ According to the CIBMTR, acute leukemias are the main indications for allogeneic transplant, accounting for more than 700 procedures per year in children and under 20-year olds in North America alone.

The stage of disease at transplant has an enormous impact on the patient's chance of cure: more advanced leukemia not only increases the chance of relapse and the toxicity of treatment expressed as "transplant-related mortality," i.e., death of the patient who is in remission.

This issue of RBHH brings us an article on the transplantation of hematopoietic stem cells in children and adolescents with acute leukemia – the experience of two important Brazilian institutions: Hospital de Clinicas, Federal

University of Parana in Curitiba, and Hospital Amaral Carvalho in Jau, Sao Paulo.⁽³⁾ A total of 208 under 19-year-old patients were transplanted over 17 years, one third using unrelated donors.

In multivariate analysis, the most important prognostic factor for transplant related mortality, disease-free survival and overall survival of children and adolescents was the stage of disease at transplant. In the CIBMTR, between 10% and 15% of patients have disease in advanced stages at the time of transplantation and in Brazilian services,⁽³⁾ 41% of 119 patients with acute lymphoblastic leukemia (ALL) and 32% of 89 patients with acute myeloid leukemia (LMA) had advanced disease, defined as third remission or greater, relapse or refractory disease.

The results reported in this study are very similar to international results: mortality associated with transplantation of 16% within 100 days, compared to 8% to 22% in the CIBMTR, and a cumulative incidence of relapse after transplantation of 40% at three years.

The overall survival for ALL patients was 43% over three years compared to 26% to 63% in related and 24% to 55% in unrelated transplantations as reported to the CIBMTR. In AML patients, the overall survival was 44% at three years, compared to 38% to 66% in CIBMTR. Myeloid refractory disease is one of the accepted indications for BMT, but only one of twenty transplant patients survives.

The cumulative incidence of transplant-related mortality was 50% over three years, which worries us a lot and points to the need for transplant centers to develop guidelines for the treatment and support and keep closer contact with the oncologists and hematologists responsible for the direct care of patients, since most of these deaths occur when the patient is not at the transplant center.

Which paths should we follow to improve the chance of curing our children? First, maintain and expand the untiring work with students, residents, doctors and community workers, in fact anyone who can help with the early diagnosis of tumors in pediatric patients. As specialists, we must increase our efforts to better characterize the leukemia we diagnose, including cytogenetic and immunophenotyping techniques. Thus, we will have concrete data to assess the risk of particular children and their response to chemotherapy, indicating the intensification of treatment when appropriate. We have known for many years that the inclusion of patients in clinical trials increases their chance of cure and we can not try hard enough for this to be effective.

As physicians who perform transplants, we can work together with oncologists, hematologists, and with the National Registry of Bone Marrow Donors (Radome) and National Registry of Bone Marrow Recipients (Rereme) to accelerate referral of children, especially those who have no compatible donor in the family. Despite much effort, the time needed to find unrelated donors in our country is still long. We have to speed this process up too, so that children do not relapse while waiting for confirmation from the donor, a situation that reduces their chance of cure.

In 2009, the Brazilian Society of Bone Marrow Transplantation (SBTMO) promoted the first meeting on the Brazilian Guidelines on Hematopoietic Stem Cell Transplantation, a vast work to review the indications for transplantation, donor selection and management of infectious complications.^(4,5) Hopefully in coming years, this work will be extended and collaborate to offer our children and teenagers increasingly better conditions to attain a cure.

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Erythrocyte index and serum ferritin in newborns

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The main consequence of iron deficiency is anemia, but this does not occur during the neonatal period.^(1,2) Thus, identifying newborns at risk for iron deficiency is very important as perinatal iron deficiency can lead to severe consequences in neurodevelopment and in iron deficiency during infancy (usually after 6 months of age).⁽²⁾ The requirement for iron is greater during periods of rapid growth and differentiation such as in the late fetal and neonatal periods.⁽³⁾

The progressive drop in hemoglobin values during the first months of life in term and premature infants has been named physiologic anemia of infancy and anemia of prematurity, respectively. In premature infants, the decline occurs more rapidly with the lowest values at 4 to 8 weeks as opposed to 10 to 12 weeks in term infants. The recovery stage of physiologic anemia depends on iron stores, but iron administration to infants does not affect the physiological drop in hemoglobin.⁽¹⁾

Iron passes into the fetus via the placenta mainly in the third trimester of pregnancy. There is risk of developing brain iron deficiency as storage iron pools become depleted in certain gestational conditions. The serum ferritin concentration has been used as a standard measurement of iron stores in infants, children and adults, but we have few data about cord serum ferritin in term and premature newborns.⁽⁴⁾ Premature infants have limited iron stores and are at risk to develop iron deficiency due to inadequate intake, frequent phlebotomy, increased erythropoiesis, rapid postnatal growth, delayed iron supplementation and low levels of iron supplementation.^(4,5)

Maternal conditions such as iron deficiency, diabetes mellitus, hypertension and smoking, and preterm birth are common causes of perinatal iron deficiency. Studies have shown that preterm newborns have lower cord serum ferritin than term babies, but levels remain within the normal range.^(4,6) A maternal ferritin concentration <12 µg/l appears to be the threshold below which fetal iron accretion is affected; 14% of full-term infants born to iron-deficient mothers have a serum ferritin concentration <30 µg/l at birth.⁽²⁾

As in other age groups, iron deficiency is more common than iron excess.⁽²⁾ As preterm infants who are submitted to multiple red blood cell (RBC) transfusions, intravenous iron therapy and aggressive enteral iron therapy have very high ferritin concentrations, it may be prudent to use appropriate iron supplementation for these patients in order to avoid iron overload. However, serum ferritin is increased in inflammatory conditions (as intrauterine growth retardation) and in neonatal hemochromatosis.^(2,4)

The article "Erythrocyte Indices and serum Ferritin in Newborns"⁽⁷⁾ published in this issue describes the