CLIPPINGS

Theme: Haematology

Gene therapy in patients with transfusion-dependent β-thalassemia (*N Engl J Med. 2018;378:1479-93*)

Gene therapy for thalassemia is keenly awaited. Results of a multinational (USA, Australia, France, Thailand and Germany) collaboration were reported this year. Mobilized autologous CD34+ cells from 22 patients (12 to 35 years of age) with transfusion-dependent β-thalassemia were obtained. The cells were transduced *ex vivo* with LentiGlobin BB305 vector, which encodes adult hemoglobin (HbA) with a T87Q amino acid substitution. The cells were then reinfused after the patients had undergone myeloablative busulfan conditioning.

At a median of 26 months (range 15-42 mo) after infusion of the gene-modified cells, all but one of the 13 patients who had a non-β^0/β^0 genotype had stopped receiving red-cell transfusions; the levels of HbA^{T87Q} ranged from 3.4 to 10.0 g/dL, and the levels of total hemoglobin ranged from 8.2 to 13.7 g/dL. The researchers concluded that gene therapy with autologous CD34+ cells transduced with the BB305 vector reduced or eliminated the need for long-term red-cell transfusions in 22 patients with severe β-thalassemia without serious adverse events related to the drug product.

The success of gene therapy for thalassemia in clinical trials is exciting news. The large-scale feasibility and a likely prohibitive cost of this potentially curative treatment are the challenges.

Improving the safety of high-dose methotrexate without access to methotrexate levels (*Pediatr Blood Cancer. 2018 May 16:e27241*)

High-dose methotrexate (HD-MTX) is an important drug for childhood acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). However, a lack of access to methotrexate levels is common in low- and middle-income countries (LMIC) – relevant for 80% of children with cancer worldwide. The team of researchers from India evaluated whether HD-MTX can be administered safely with extended hydration and leucovorin rescue, with monitoring of serum creatinine and urine pH.

Patients with B-cell ALL, T-cell ALL or T-NHL were administered 3 and 5 g/m^2 of MTX (24 h infusion), respectively. Six doses of leucovorin (15 mg/m^2/dose), instead of recommended three (for optimally reduced levels) at standard timing (42 h from start of HD-MTX) were administered. Hydration was continued for 72 h, instead of the recommended 30 h. Serum creatinine and urine pH were measured at baseline, 24 h and 48 h. The volume of hydration was increased for a serum creatinine >1.25 times the baseline. The study included 100 cycles of HD-MTX in 53 patients: B-ALL 25 patients (51 cycles), T-ALL 16 patients (28 cycles), T-NHL 10 patients (18 cycles), and relapsed ALL 2 patients (3 cycles). Toxicities included mucositis (32%), diarrhea (10%) and febrile neutropenia (9%). The authors concluded that it is safe to administer 3 or 5 g/m^2 of MTX (24 hr infusion) without measuring MTX levels, with extended hydration, additional doses of leucovorin, and monitoring of serum creatinine and urine pH.

Emicizumab prophylaxis in hemophilia A (*N Engl J Med. 2018;379:811-22*)

Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis. In a phase-3 multicenter trial, prophylaxis with emicizumab was investigated in persons who have hemophilia A without factor VIII inhibitors.

Researchers randomly assigned 152 participants ≥12 years of age, who had been receiving episodic treatment with factor VIII, to receive a subcutaneous maintenance dose of 1.5 mg/kg/week of emicizumab (group A) or 3 mg/kg every 2 weeks (group B) or no prophylaxis (group C). The annualized bleeding rate was 96% lower in group A and 97% lower in group B (P<0.001 for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events in comparison to those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis (P<0.001). The authors concluded that emicizumab prophylaxis led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A.

Vitamin D deficiency and mild to moderate anemia in young North Indian children: A secondary data analysis *(Nutrition. 2018;57:63-8)*

The aim was to examine the association between vitamin D deficiency and anemia status among young children in the resource-poor setting of northern urban India. Data from a randomized controlled trial of daily supplementation with folic acid, vitamin B_{12}, or both for 6 months in children 6-30 mo of age conducted in Delhi was utilized. Serum vitamin D status, hemoglobin, plasma vitamin B_{12}, folate, soluble transferrin receptor, and homocysteine levels were measured at baseline. Children with severe anemia (hemoglobin <7 g/dL) were excluded.

25-hydroxyvitamin-D (25OHD) concentration was measured for 960 children. Of these children, 331 (34.5%) were vitamin-D deficient (25OHD <10 ng/mL). Approximately 70% of the enrolled children were anemic with 46% having moderate (hemoglobin 7-9.9 g/dL) and 24% mild (hemoglobin 10-10.9 g/dL) anemia. Vitamin D deficiency was associated with moderate anemia among young children, and the effect was independent of iron deficiency.

The causal association of vitamin D deficiency with anemia risk still remains debatable. The role of vitamin D in risk for anemia needs to be examined in further studies.

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