**Education Continued from Page 3**

**2015**

2. Iron: Too Little or Too Much? - Brigitta Mueller, MD, FAAP
3. Clots and Kids: An Increasing Problem – Shannon Carpenter, MD, FAAP

In addition, the Section has the opportunity to provide content for the AAP News Focus on Subspecialties column on an annual basis. This content focuses on pediatric hematology/oncology topics that are of broad interest to general pediatricians and other subspecialists. Thank you to Dr. Denise Adams for collaborating with the Dr. Marilyn Liang of the Section on Dermatology in writing the article, “Treatment of vascular anomalies advancing, but more research needed” (http://aapnews.aappublications.org/content/35/10/12.full.pdf+html) for the October edition. A listing of the other articles that have been contributed by SOHO can be found on the website at: http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Pages/Newsletters-and-Publications.aspx

Finally, www.HealthyChildren.org is the Academy's website for parents and caregivers. One of the goals of the subcommittee is to review and revise current PHO content and explore the development of new articles. We plan to engage in this process in 2015.

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**Hot Papers in Pediatric Hematology/Oncology**

**Reviewed by:** Mary Jane Hogan, MD, FAAP, Assistant Clinical Professor, Pediatric Hematology Oncology, Yale University School of Medicine, New Haven, Connecticut.


Between April 2012 and February 2014, 25 children with relapsed or refractory acute lymphoblastic leukemia from Children's Hospital of Philadelphia, and 5 adults with similar disease from University of Pennsylvania School of Medicine were infused with autologous chimeric antigen receptor-modified T cells targeting CD 19 (CTL019). The study found that 27 of 30 patients (90%) experienced complete remissions, including 15 treated with prior hematopoietic stem cell transplant (SCT) and 2 treated with prior blinatumomab, a CD19-directed bispecific antibody. Of the 27 patients who achieved a complete remission, 5 withdrew from the study for alternate therapy, three of whom were treated with allogeneic SCT and in remission 7 to 12 months after CTL019 infusion.

Fifteen patients achieved a sustained remission with no further therapy at a median follow-up of seven months. The probability of 6-month event-free survival was 67% (95% CI, 51% to 88%) and overall survival was 78% (95% CI, 65% to 95%). Probability of six-month CTL019 persistence was 68% (95% CI, 50 to 92%) and relapse-free B cell aplasia was 73% (95% CI, 57 to 97%). Sustained remissions for up to 2 years, observed in these 15 patients, were associated with quantitative PCR-detectable CTL019 sequences and B cell aplasia.

All patients experienced cytokine release syndrome. Eight patients (27%) developed severe symptoms which were associated with higher disease burden and effectively treated with tocilizumab, an IL-6 receptor antibody. Thirteen patients (43%) had neurologic toxicities, ranging from febrile delirium to global encephalopathy, which completely resolved without additional intervention or apparent chronic implications.


Investigators from multiple, international research centers, led by St. Jude Children's Research Hospital, obtained microarray gene-expression profiling of 1725 individuals, ages 1 to 39, diagnosed with precursor B-cell acute lymphoblastic
leukemias (ALL) to determine the frequency, diversity and tyrosine kinase inhibitor responsiveness of genetic alterations in Philadelphia chromosome-like ALL (Ph-like ALL). Individuals with Ph-like ALL do not possess the BCR-ABL1 fusion protein from the t(9:22)(q34;q11.2) Philadelphia chromosome, but have a similar gene-expression profile, alterations of the lymphoid transcription factor gene, IKZF1, and poor outcomes as patients with BCR-ABL1 positive ALL. Next-generation sequencing to identify genetic alterations that cause Ph-like ALL was performed on 154 patients. Mouse pre-B cells and xenografts of human Ph-like ALL were examined for functional effects of fusion proteins and tyrosine kinase inhibitor efficacy.

The frequency of Ph-like ALL increased with age and was associated with poor survival compared to other precursor B-cell ALL. Overall, 264 (15.3%) patients possessed Ph-like ALL, ranging from 10% of children, ages 1 to 9, with standard risk ALL, to 27% of adults, ages 21 to 39, with ALL. Among patients with Ph-like ALL, 5 year overall survival rate for children, adolescents and young adults was 62%, compared to 91% for the same ages without Ph-like ALL.

Alterations involving kinase signalling or cytokine receptor activation were discovered in 91% of patients with Ph-like ALL including rearrangements in ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, NTRK3, PDGFRB, PTK2B, TSLP, or TYK2 and sequence mutations in FLT3, IL7R, or SH2B3. New subgroups of Ph-like ALL sensitive in vitro to dasatinib included ABL1, ABL2, CSF1R, and PDGFRB fusions, ruxolitinib-sensitivity included EPOR and JAK2 rearrangements and crizotinib-sensitivity was associated with ETV6–NTRK3 fusion. Additional investigations in older adult Ph-like subtypes and clinical trials identifying Ph-like ALL are needed to assess the efficacy of adding tyrosine kinase inhibitors to current therapy regimens.


An open-label, randomized phase III study by investigators from Blood and Marrow Transplant Clinical Trials Network was conducted to compare outcomes between children with hematologic cancer undergoing double unit (n=111) or single-unit cord blood transplantation (n=113) after a uniform myeloablative conditioning regimen and graft-versus-host disease (GVHD) prophylaxis. Between December 2006 and February 2013, children, ages 1 to 21 years, diagnosed with acute myelogenous leukemia, acute lymphocytic leukemia, acute biphenotypic leukemia, myelodysplastic syndrome or chronic myeloid leukemia received cord blood HLA matched to at least 4 of 6 different loci, with the first unit at least 2.5 x 10^7 nucleated cells /kg of body weight, and the second unit, at least 1.5 x 10^7 nucleated cells/ kg of body weight. All patients received a conditioning regimen of fludarabine, total body irradiation, and cyclophosphamide, and post transplant GVHD prophylaxis of cyclosporine for 6 months with subsequent tapering, and mycophenolate mofetil for 45 days (or longer depending upon GVHD status).

Both groups were matched for sex, age, cytomegalovirus status, disease type, self-reported race, degree of donor-recipient HLA matching, and status at transplantation. Overall survival at 1 year was 65% (95% CI, 56 to 74) for double-unit recipients and 73% (95% CI, 63 to 80) for single-unit recipients. Hazard ratio for mortality was 1.34 (95% CI: 0.86 - 2.09; P = .20) for double-unit vs single-unit recipients. There were no differences in rates of disease-free survival, neutrophil and immunologic recovery, transplantation-related mortality, relapse, infections, acute and chronic GVHD. However, single unit recipients had higher (76% vs 65%; P = .04) and sooner platelet recovery (58 days vs 84 days) than those who received double units. In addition, one unit recipients had lower rates of grade III and IV acute and chronic GVHD (13% vs 23%; P = .02) than two unit recipients. The authors conclude that given the difficulty finding in HLA compatible donors, double unit cord blood transplantation did not confer significant additional benefit over single unit.

Reviewed by: Taizo Nakano, MD, FAAP, Assistant Professor, Pediatrics, Center for Cancer and Blood Disorders Children's Hospital Colorado, University of Colorado School of Medicine


In hemophilia B, a small increase in the factor IX percentage can move a patient from the severe to moderate deficiency category, thereby greatly reducing both the incidence of severe bleeds and use of factor product. This same principle...
behind prophylactic factor replacement that is now standard care for severe hemophilia patients also drives the pursuit of gene therapy. The goal is to finally replace the chronic administration of recombinant factor products with a single infusion resulting in long-term expression of factor IX. The study carried out by Nathwani et al. represents the efforts of an international collaboration of hematologists to move gene therapy from the bench to the bedside and provide a less invasive, less expensive, and importantly, a curative approach to hemophilia B.

Their use of a novel self-complimentary adeno-associated serotype virus (AAV8) led to successful in vivo expression of factor IX in a pilot study previously published (N Engl J Med 2011;365:2357-2365). Building on that success, the current study evaluates the stability of transgene expression and the long-term safety in 10 patients with severe hemophilia B. The manuscript reports long-term, albeit low level, therapeutic factor IX expression and clinical improvement in all 10 patients infused with a single dose of AAV8 vector. Furthermore, no late toxic effects were reported after 3 years of follow up. Their success represents an important milestone in the pursuit of gene therapy that could translate into applications for numerous blood protein deficiencies.


The past decade produced a number of monumental trials that reshaped the care of pediatric patients with sickle cell anemia. With a focus on preventative care, the results of these trials were recently summarized in an evidence-based publication, Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members (JAMA 2014;312(10):1033-48). Beginning the next chapter to reshape sickle cell care, Debaun et al. aimed to study a persistent concern in the sickle cell community, the silent cerebral infarct. Though it is known to increase risk for symptomatic stroke, poor academic achievement, and lower IQ, we lack standardized guidelines to diagnose, monitor and treat this common neurologic injury.

The Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) set out to determine whether blood-transfusion therapy can prevent an end-point of stroke or new or enlarged silent cerebral infarct. The authors carried out a multicenter, randomized trial that assigned 196 children with sickle cell anemia-related silent cerebral infarcts to either receive standard observational care or blood-transfusion therapy. After a median follow up of 3 years, 6% of children in the transfusion group experienced an end-point complication compared to 14% of children in the observation group. They conclude that blood-transfusion therapy significantly reduces the incidence of recurrent cerebral infarct in children with sickle cell anemia and propose a potential opportunity to impact the long-term burden of neurologic injury in this patient population.


Recognizing the rapid progress in recent years to understand primary thrombotic microangiopathy (TMA), the authors present a thorough review to better define and classify TMA syndromes. They summarize our current understanding of the pathogenesis, management, and outcomes of these syndromes and move away from ambiguous terms like “atypical” and “idiopathic”. Nine primary disorders are presented taking note of important historical milestones that help to identify both their common clinical features and unique differences. A focus on both acquired and hereditary complement-mediated TMA provides a platform for continued discussion on the role of anticompliment therapy. Overall, the review highlights how the field's great successes have reduced mortality and revealed previously unrecognized long-term morbidities.