
Investigators from European, Canadian and U.S. institutions performed a three-stage genome-wide association study combined with biological functional analysis in 456 childhood cancer survivors treated with similar chemotherapy regimens, to identify a germline variant correlating with anthracycline-induced cardiotoxicity. Genome-wide single-nucleotide polymorphism analyses were completed on blood DNA samples of cases (n=73) and controls previously diagnosed with cancer ≤ 18 years old and at least 5 years after treatment. Cases were defined as having shortening fractions (SFs) of ≤24% or signs of cardiac compromise while controls had SFs ≥ 30% and no symptoms of cardiac compromise according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (CTCAEv3). Factors known to affect cardiac function such as age at treatment, cumulative anthracycline dose, radiotherapy, and a diagnosis of acute lymphoblastic leukemia, rhabdomyosarcoma or Ewing’s sarcoma were included as covariates for logistic regression analysis.

A nonsynonymous variant, rs2229774, p.Ser427Leu, in the *RARG* (retinoic acid receptor gamma) gene had a significant association with anthracycline-induced cardiotoxicity (OR 4.7, 95%CI 2.7-8.3, *P*=5.9x 10^-8). RARG has been shown to bind to topoisomerase IIβ (*Top2b*) promoter and to be highly expressed in the heart. Anthracyclines bind and inhibit topoisomerase II involving *Top2b*. This RARG Ser427Leu variant did not repress *Top2b* expression and the resulting higher levels of *Top2b* are consistent with increased susceptibility to anthracycline-induced cardiotoxicity. The authors conclude that future clinic trials with a larger study population may be helpful to establish risk assessment in anthracycline sensitive patients with the rs229774 variant in *RARG*.


Investigators from the University of Michigan studied the feasibility and utility of integrative clinical sequencing and genetic counseling in the clinical management of children with relapse, refractory or rare malignancy. This single-center, prospective, consecutive case series involved 91 patients (median age 11.5 years, range 0-22 years), 28 with hematologic malignancies and 63 with solid tumors, between May 2012-October 2014. Subjects’ tumor and germline (from blood mononuclear cell) DNAs were tested using integrative clinical exome sequencing and tumor RNA underwent transcriptome sequencing.

A precision medicine tumor board discovered potentially actionable findings in 42 of 91 (46% of) patients that could change cancer management involving 54% with hematological
malignancies and 43% with solid tumors. Individualized actions were actually taken in 23 of 42 children (54%) which included a change in treatment for 14 patients (15% of patients overall) and genetic counseling for future risk in 9 patients. Of those undergoing treatment changes, 9 experienced partial or complete clinical remission up to 21 months. There was no control group to compare clinical outcomes of this group with those receiving standard care. The authors speculate that newly discovered tumor non-specific gene fusions, lack of available pediatric drugs for off-label use, and length of time for sequencing results, in this high risk population, made it difficult to pursue actionable findings.

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

Histiocytic Disorders:


Continuing their efforts to better understand and treat Langerhans cell histiocytosis (LCH), the international Histiocyte Society recently published the results of a phase II trial designed to study LCH patients with the worst prognosis and survival; patients with refractory, risk-organ-positive disease. 27 patients were enrolled over a 5-year enrollment period to receive two courses of high-dose cladribine and cytosine arabinoside. The authors report an overall response rate of 92% and long-term survival rate of 85%. The findings provide optimism for patients with refractory multisystem disease with risk organ involvement. The authors developed a disease activity score (DAS) to better evaluate patient status that provides the community a more comprehensive definition of disease response.

Hemoglobinopathies:


Severe cardiac siderosis has the potential to result in heart failure and fatal arrhythmias. We’ve learned to better screen for iron overload and aggressively chelate as necessary through a series of influential studies carried out on the pediatric β-thalassemia major population. The American Heart Association summarized our current understanding of how to manage iron overload in a recent publication that highlights the utility of Deferiprone in the management of severe cardiac siderosis (Pennell et al. Cardiovascular Function and Treatment in β-Thalassemia Major, 2013). In this most recent study by Totardi et al, the safety and efficacy of the Deferiprone and Deferasirox combination was evaluated in 36 iron overloaded patients. Overall, they demonstrate safety and efficacy when compared to monotherapy controls. The advantage of this regimen is that both agents are available in the oral form and at lower cost than continuous IV Desferrioxamine standard of care.
Hemostasis & Thrombosis:


Patient families and the international pediatric hemophilia community have been eagerly awaiting the results of the BAX 855 trials. Baxalta’s pegylated full-length recombinant FVIII was developed to increase factor half-life and reduce factor administration. This publication summarizes both the phase I and pivotal clinical studies recently completed on BAX 855. The collaborative achieved their primary end point of identifying a safe and efficacious product and have begun to answer the question on every parent and physician's mind; can BAX 855 show large-scale equivalence to standard of care. Patients in the prophylaxis group (twice weekly infusions) demonstrated a similar reduced annualized bleeding rate (90% reduced) compared with the on-demand group and with those receiving standard rFVIII prophylaxis (three times weekly infusions).

Vascular Anomalies:


The basic pathophysiology of many pediatric vascular malformations and tumors remains incompletely understood. The field quite accidentally determined that propranolol has significant efficacy to induce regression of pediatric infantile hemangiomas. The authors of this publication studied the changes in protein expression before and after the administration of propranolol in a cell line model of infantile hemangioma. They determined that propranolol down regulates the PI3K/Akt/eNOS/VEGF pathway, which inhibits cell cycle progression in endothelial cells and provides a novel explanation for its antiangiogenic properties. A better understanding of the pathophysiology of disease not only helps justify the utility of the medication, but may help identify additional therapeutic targets.