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Journal Club: The Lightning Rounds

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Introduction

Journal Club: The Lightning Rounds is a synopsis of current literature in Pediatric hematology & oncology. The articles have been selected from clinical and scientific journals, and represent high impact research that may influence the current and future practice of pediatric hematologist and oncologists.

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Journal Club – The Lightning Rounds

Section 1. General Hematology, Thrombosis & Transfusion Medicine

Optimizing chronic transfusion therapy for survivors of hemoglobin Barts hydrops fetalis

Amid A, (2016) Blood, *(Link to abstract)*

Ali Amid, Melanie Kirby-Allen, and Isaac Odame evaluated a new transfusion strategy in hemoglobin Barts hydrops fetalis or homozygous α^{0}-thalassemia. They described that a traditional transfusion strategy adopted from transfusion-dependent beta-thalassemia targeting a hemoglobin >100 g/L led to persistent chronic hemolysis, splenomegaly, elevated HbH, and high erythropoietin as a marker for tissue hypoxia. The HbH percentage ranged from 24 to 64%. The authors estimated that the functional hemoglobin was in the range of 43 to 79 g/L. The authors suggest that homozygous α^{0}-thalassemia is a hemolytic disease with robust erythropoiesis in contrast to transfusion-dependent beta-thalassemia and therefore a more aggressive transfusion strategy might be needed to suppress HbH formation. A new transfusion strategy aiming at hemoglobin levels >100 g/L and HbH percentages <15% was implemented leading to decrease in spleen size, reticulocyte counts, hemolytic parameters, and erythropoietin levels. The more aggressive transfusion protocol led to an increase in red blood cell transfusion volume form 208 ml/kg per year to 286 ml/kg.

❖ Implementation of a more aggressive transfusion protocol targeting HbH<15% and hemoglobin 100 g/L in hemoglobin Barts hydrops fetalis led to decrease in hemolytic parameters, spleen size, and markers of tissue hypoxia but this study did not report on clinical benefits. It is unclear if the increase in transfusion burden and iron overload needing increase in chelation is outweighed by clinical improvements.

Eculizumab salvage therapy for delayed hemolysis transfusion reaction in sickle cell disease patients

Dumas G, (, 2016), Blood, (*Link to abstract*)

The authors analyzed the effect of eculizumab, an anti-C5 monoclonal antibody, on three patients with Sickle Cell Disease (SCD) affected with delayed hemolytic transfusion reaction (DHTR) after blood transfusions. Administration of 2 doses of eculizumab led to reduction of hemolysis and vasculopathy. Despite normal C3 levels, there were signs of terminal complement activation in these patients providing a basis of the mechanisms implicated.

❖ Eculizumab showed efficacy on delayed hemolytic transfusion reactions in three SCD-patients and can be considered in severe cases.

Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications

Hazendonk HCAM, (2016) JTH, (*Link to abstract*)

Patients with severe hemophilia A undergoing surgery need factor replacement to reduce the risk of bleeds, under- and overdosing is a known issue. This article assessed retrospectively 119 patients (75 adults and 44 children) with severe hemophilia A (factor VIII deficiency <0.05 U/mL) and their perioperative management. 198 elective minor and major surgical events were included. The authors found that 7-45% of achieved FVIII levels on postoperative days were under- and 33-75% overdosed. 44% of factor VIII administered might have been spared. Blood group O was predictive of underdosing and these patients presented more bleeding complications (OR 2.0). Patients with other blood groups were at higher risk of overdosing (OR 1.5). When looking at the bleeding complications, the vast majority was found in the adult population.

❖ Severe hemophilia A patients with blood group O seem to be at a higher risk of underdosing than patients with other blood groups and had more bleeding episodes. Unfortunately, the number of pediatric patients does not allow us to draw this conclusion in the pediatric subset as well.

Diagnostic value of immunoassays for heparin-induced thrombocytopenia: a systematic review and meta-analysis

Nagler M, et al. Blood. 2016;127(5):546–557. (*Link to abstract*)

Heparin-induced thrombocytopenia (HIT) is in the pediatric population a rare but potentially life-threatening adverse event of heparin-treatment. Its diagnosis relies on clinical assessment and identification of specific heparin-induced PF4 antibodies. This systematic review and meta-analysis compares different PF4 immunoassays used to identify HIT. 49 publications with 128 test evaluations in >15 000 patients. The authors found significant differences in sensitivity and specificity. In summary, only 5 tests showed high sensitivity (>95%) and high specificity (>90%): polyspecific enzyme-linked immunosorbent assay (ELISA) with intermediate threshold, particle gel immunoassay, lateral flow immunoassay, polyspecific chemoluminescent immunoassay (CLIA) with high threshold, and IgG-specific CLIA with low threshold.

❖ According to this analysis, only 5 immunoassays exhibit high sensitivity and specificity to ascertain the diagnosis of HIT; clinicians should be aware of this limitation and talk to the lab if there is a lab test result conflicting with the clinical picture.

Secondhand smoke is associated with more frequent hospitalizations in children with sickle cell disease.

Sadreameli, SC, (2016) American Journal of Hematology, (Link to Abstract)

This is a retrospective and prospective cohort study evaluating the association between cigarette smoke exposure, quantified by measuring the salivary cotinine levels, and incidence of hospital admissions in children with sickle cell disease. Fifty children and young adults with sickle cell disease were enrolled in the study. Questionnaires were administered to determine self-reported/parent-reported smoke exposure and saliva samples were obtained from study subjects to determine cotinine, the major nicotine metabolite, levels. A cotinine level > 0.5 ng/mL was considered to be indicative of smoke exposure, with a level > 10 ng/mL indicative of a primary smoker.

The incidence risk ratio (IRR) for children with any smoke exposure (increased cotinine levels) for hospital admission was 3.7, with those exposed to second hand smoke with an IRR of 4.3. Risks of acute chest crisis and pain crises were also significantly increased in those children found to have any smoke exposure. One limitation of this study was that there was a significant age difference between patients being cotinine positive and negative, which might impact the findings.

❖ Both primary and secondary exposure to tobacco smoke increases the risk of hospitalizations in children with sickle cell disease, so it is vital that we regularly screen this population for tobacco smoke exposure and educate families about the associated risks.

Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents

Wlodarski M, (2016), Blood, (Link to abstract)

Myelodysplastic syndrome is rare in children and there is growing evidence of genetic predispositions leading to its occurrence. GATA2 germline mutations were identified to be associated with pediatric MDS. The authors of this study are part of the EWOG-MDS group, a large European consortium overseeing a large database of pediatric patients with MDS, SAA, and JMML. They analyzed 426 children and adolescents with primary MDS and 82 cases with secondary MDS from two prospective studies. The found germline GATA2 mutations to be associated with higher grade MDS and older age: 15%, 7%, 0%, 0% for advanced primary, overall primary, secondary MDS, and SAA respectively. There was a correlation with monosomy 7 and older age: patients 12-19 years with monosomy were affected in 72% of cases compared to 7% 0-6 years. Survival was not altered in patients with or without GATA2 germline mutations.

❖ GATA2 germline mutations are associated with de novo MDS in the pediatric population and are the most common genetic predisposition without impact on survival.

Occult hemorrhage in children with severe ITP.

Flores, A (2016) American Journal of Hematology, (Link to Abstract)

Immune thrombocytopenia (ITP) is one of the most common causes of severe thrombocytopenia in the pediatric population and is associated with the risk of severe bleeds, although these are encountered infrequently. This is a prospective cohort study investigating the incidence of occult hemorrhage in children with severe immune thrombocytopenia (ITP), defined as a platelet count < 10. Each enrolled patient underwent a bleeding severity assessment, urinalysis, fecal occult blood testing and non-contrast brain MRI upon initial diagnosis or symptomatic relapse.

27% of patients were found to have occult hematuria, and one child was identified with microbleeding in the superficial cortex of the left frontal lobe. However, no association was found between occult hemorrhage and overt bleeding manifestations or increased risk of subsequent bleeds. Further study is needed to elucidate the potential risks of occult bleeds in this population.

❖ Children with severe ITP are at risk of occult bleeds, which pose a potential risk to this population. These seem unrelated to major bleeds though and therefore screening seems unnecessary according to current knowledge.

REVIEWS/ PERSPECTIVES

Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology

Zhang D, (2016), Blood, (Link to abstract)

Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease

Telen MJ, (2016), Blood, Link to abstract

Pathophysiology and treatment of pulmonary hypertension in sickle cell disease

Gordeuk VR, (2016), Blood, Link to abstract

Central nervous system complications and management in sickle cell disease

DeBaun MR, (2016), Blood, Link to abstract

Genetic treatment of a molecular disorder: gene therapy approaches to sickle cell disease

Hoban MD, (2016), Blood, Link to abstract

How I treat acute graft-versus-host disease of the gastrointestinal tract and the liver

McDonald GB, (2016), Blood, Link to abstract

Early warning and prevention of pneumonia in acute leukemia by patient education, spirometry, and positive expiratory pressure: A randomized controlled trial.

Moller, T, (2016) American Journal of Hematology, (Link to abstract)

This study is a randomized control trial studying the applicability of daily spirometry as an early warning tool for pneumonia in patients undergoing treatment for AML, and also explored if the addition of positive expiratory pressure (PEEP) might be effective in preventing the development of pneumonia. 80 adult AML patients were enrolled on the trial and were randomized to daily spirometry with or without PEEP. A FEV1 value of 76-80% was found to be highly sensitive and specific for pneumonia development, and there was a significant decrease in the incidence of pneumonia in the patients who were randomized to the PEEP arm (2.17 per 1000 days vs 6.52 per 1000 days, P = 0.021). The authors suggest that daily self-administered spirometry along with the use of PEEP should be part of the standard of care for AML patients undergoing induction chemotherapy.

❖ Daily self-administered spirometry may be a useful early warning tool for pneumonia in patients undergoing treatment for AML, and the addition of positive expiratory pressure may help prevent episodes of pneumonia. This approach is not feasible in young pediatric patients and the usefulness in children has not been proven.

Umbilical cord blood–derived T regulatory cells to prevent GVHD: kinetics, toxicity profile, and clinical effect

Brunstein CG, (2016) Blood, (Link to Abstract)

In this article, the authors examined the rate of GVHD in eleven adult patients undergoing double umbilical cord blood (UCB) stem cell transplantation receiving additional UCB-derived T regulatory cells on day +1 from a third UCB graft 4-6/6 matched. The rate of GVHD was compared to contemporary controls (n=22). The authors found low grade II-IV GVHD on day 100 of 9% in the treatment cohort compared to 45% in controls (p=0.05). At 1 year there were no patients with cGVHD in the treatment group compared to 14% in controls (no statistical comparison provided). No differences in treatment-mortality or relapse were seen.

❖ In double UCB-HSCT of adult patients with hematological malignancies, the transfusion of T reg from a third UCB graft resulted in low acute and chronic GVHD rates although the numbers in this study were small and therefore definite conclusions cannot be drawn. It would be interested to see a similar approach in children.

Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation.

van der Sluis IM, (2016) Haematologica, (Link to abstract)

Asparaginase is an essential component in the treatment of childhood ALL. This article is a consensus of expert opinions on the role of serum asparaginase level assessment, indications for switching asparaginase preparation, and monitoring after change in asparaginase preparation.

❖ Routine asparaginase activity monitoring for ALL patients has been started in Sickkids recently, it is important to understand the rationale and clinical implications.

LIN28B overexpression defines a novel fetal-like subgroup of juvenile myelomonocytic leukemia

Helsmoortel HH, (2016) Blood, (Link to abstract)

Juvenile myelomonocytic leukemia (JMML) is a subtype of leukemia predominantly seen in young children with an aggressive course and poor survival. The authors used gene expression profiling in 82 patients (first 44 children in a discovery cohort, then 38 patients in a validation cohort) affected with juvenile myelomonocytic leukemia (JMML). RNA was analyzed by microarray profiling and identified a subgroup characterized by high *LIN28B* expression in roughly half the analyzed patients. *LIN28B* is known as an oncofetal gene regulating self-renewal of embryonic, fetal, and cancer stem cells, suggesting a role in stem cell malignancies. Affected patients expressed high HbF levels but only rare cases of monosomy 7, an event seen in about 25% of all JMML patients. The authors termed this subtype "fetal-like" and found overexpression of genes involved in fetal hematopoiesis and stem cell self-renewal. This subgroup had a worse outcome than other patients, although this was not an independent from other risk factors.

❖ The authors describe high *LIN28B* expression as a feature of JMML found in roughly half the cases, which correlated to indicators of fetal hematopoiesis and poor survival. This feature did not pan out to be an independent risk factor though. *LIN28B* still might be an interesting target as it is under assessment for other cancers and might be an interesting pathway for future treatment protocols.

Genetic risk factors for the development of osteonecrosis in children under age 10 treated for acute lymphoblastic leukemia

Karol SE, et al. Blood. 2016;127(5):558–564. (Link to abstract)

This analysis looks at genetic risk factors for osteonecrosis in patients with ALL, which is a major toxicity with long-term morbidity in patients undergoing treatment for ALL. Age >10 years is a well-known risk factor, but 40% of children affected by osteonecrosis are <10 years. This article evaluated the germline genotype by using whole exome sequencing of 369 patients <10 years with 82 being affected with osteonecrosis. Variants close to three genes (*BMP7, PROX1-AS1*, and *GRID2*) were identified as risk factors. Please see as well a previous article from this author looking at genetic risk factors for osteonecrosis in patients with ALL in a cohort of patients from

pediatric treatment protocols in Blood. A SNP in the glutamate receptor *GRIN3A* locus was identified as a risk factor for osteonecrosis (Karol SE, et al. Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia. Blood. 2015;126(15):1770–1776). Interestingly, the mutation previously identified in a mixed cohort of patients <10y AND >10 years did not show up as a risk factor in this cohort of patients exclusively <10 years.

❖ According to this and other studies, there are genetic risk factors to develop osteonecrosis when undergoing treatment for ALL. It is too early to include this knowledge to assess the risk of developing this complication. Furthermore, it is unclear what impact this knowledge could have on treatment (modification of steroids?).

Proteasome inhibitors induce FLT3-ITD degradation through autophagy in AML cells

Larrue C, (2016) Blood, Link to abstract)

FLT3-ITD positive AML is a subset of AML with poor prognosis. The authors examined the effect of bortezomib, a proteasome-inhibitor, on FLT3-ITD positive AML cells in vitro. The authors found that FLT3-ITD positive cells were more sensitive to bortezomib than wild-type cells. This effect was stronger, the higher the FLT3-ITD expression was. The mechanisms identified leading to this sensitivity were through cytotoxic autophagy. FLT3-ITD molecules were identified within autophagosomes which led to MAPK/ ERK, PI3K/ AKT, and STAT5 pathway inhibition and ultimately to cell death. Bortezomib treatment led to sensitivity to a second-generation tyrosine kinase inhibitor with high FLT3 selectivity (quizartinib) in cells that were found to be resistant prior to bortezomib application. Finally, in xenograft mice models, bortezomib led to induction of autophagy and improved survival.

❖ The results of this study provide a theoretical basis to consider treatment with bortezomib and a tyrosine-kinase inhibitor with high FLT3 selectivity in patients with FLT3-ITD positive AML.

Chimeric antigen receptor-modified T cells derived from define CD8(+) and CD4(+) subsets confer superior antitumor reactivity in vivo.

Sommermeyer D, (2016) Leukemia,(Link to abstract)

CD 19 CAR T-cells is a new and promising approach to treatment of B-cell malignancies. It is known that prior chemotherapy can alter T-cell numbers. In current trials, patients receive unselected CAR T-cell products with large variation in composition of T-cells subsets (CD4+ /CD8+ naïve, central memory, effector memory).

The authors compared the in-vivo potency of CD19 CAR T-cell products prepared from pre- sorted/purified subsets of T-cells. They found that a combination of CAR T-cells derived from CD8+ central memory T-cells and CD4+ naïve / central memory T-cells showed synergistic effect, with superior proliferation of the CD8+ CAR T-cells with enhanced anti-tumor effect. They concluded that the composition of CAR-T-cell products influences function and therapeutic efficacy.

❖ This study helps to understand one of the variables which affect the efficacy and toxicity of CAR T-cells in individual patients and across studies. The advancement of cell selection methods should enable production of CAR T-cell products with specific cell composition and doses in future.

Post-transplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation

Mielcarek M, (2016) Blood, (Link to abstract)

GVHD post HSCT is associated with major morbidity and hampers survival. The authors analyzed in a prospective trial of 43 patients (pediatric n=5) with high-risk hematologic malignancies treated on a novel protocol with myeloablative conditioning regimens (TBI containing with 12Gy radiation, n=18, and non-TBI regimen FluBu, n=25) and post-HSCT high-dose cyclophosphamide (50mg/kg on days 3 and 4 post-HSCT). Additional GVHD prophylaxis consisted of cyclosporine A starting on day +5. Graft source was exclusively peripheral stimulated blood. The authors found a relatively high incidence of acute GVHD grade II of 77% but a low incidence of grade III-IV acute GVHD of 0% and an incidence of chronic GVHD needing systemic immunosuppression of 16%. Non-relapse mortality after 2 years was 14%, relapse-mortality was 17%. TBI was associated with lower relapse incidence but higher cGVHD, whereas BuFlu was associated with lower incidence of cGVHD and lower overall survival (with the two groups being distinct in terms of their age and recurrence risks).

❖ Post-HSCT high-dose cyclophosphamide was tolerated post myeloablative conditioning regimens and led to a relatively low incidence of cGVHD needing systemic immunosuppression in a mixed adult/ pediatric population.

CD33 Expression and Its Association with Gemtuzumab Ozogamycin Response: Results from AAML0531

Pollard, JA, (2016) Journal of Clinical Oncology (Link to abstract)

Gemtuzumab ozogamycin (Mylotarg) is a humanized antibody against CD33 with efficacy in acute myeloid leukemia at the expense of marked associated toxicity. This is a secondary analysis of the AAML0531 data which randomized children to standard therapy with or without gemtuzumab in induction and in consolidation. This study assessed whether CD33 expression in AML cells was associated with outcome in those who received gemtuzumab. Indeed, those with the highest expression had the lowest relapse with gemtuzumab and a better EFS with this drug whereas EFS was the same in those who got the drug but had low CD33 expression compared to those who didn't get the drug.

❖ Gemtuzumab has a very important toxicity profile; targeting patients who will get the most benefit should therefore be the goal. This study indicates that CD33 expression level should probably be measured before allocating children to this treatment.

Quality of Life and Mood Predict Posttraumatic Stress Disorder After Hematopoietic Stem Cell Transplantation.

El-Jawahri, A (2016), Cancer, (Link to abstract)

Hematopoietic stem cell transplantation (HSCT) is a high-intensity treatment which is associated with an important risk of long-term morbidity and mortality. This study looked at 90 patients over 18 years undergoing allogeneic and autologous transplants. Various tools to measure quality of life (QOL) were used to assess for post-traumatic stress disorder (PTSD) symptoms at 6 months after transplant. QOL had returned to baseline in most patients at 6 months but 28.4% met criteria for PTSD and 43.3% for depression. Changes of QOL and depression scores within hospitalization predicted PTSD and QOL impairment at 6 months. The authors suggest early intervention during the HSCT procedure to reduce the risk of ongoing QOL impact.

❖ In adults, a significant proportion of patients experience depression and reduced QOL during transplant and PTSD and depression post HSCT.

Influence of Cranial Radiotherapy on Outcome in Children with Acute Lymphoblastic Leukemia Treated with Contemporary Therapy

Vora, A, (2016) Journal of Clinical Oncology (Link to abstract)

Children with acute lymphoblastic leukemia (ALL) are at risk for relapse from the CNS, and therefore CNS directed therapy has become a mainstay of ALL treatment. Cranial radiotherapy (CRT) is declining in use and gets replaced increasingly by intrathecal therapy and chemotherapy with CNS penetrance such as high dose methotrexate. This is a meta-analysis of the results from all upfront ALL trials in 10 co-operative groups between 1996-2007 looking at whether CRT changes the rate of relapse. None of the trials were randomized to answer this question and each had slightly different indications for using CRT. Overall, there was no difference in outcome between those who received CRT and those who did not. There was a higher incidence of CNS relapse in CNS3 patients who did not get CRT but the overall relapse rate was not different regardless of therapy. The authors suggest that CRT may no longer have a role in the context of modern therapy.

❖ Is this study the straw that breaks the back of CRT in ALL? In this metaphor, the St Jude's Total XV study (Pui, NEJM 2009) was a whole load of straws that started this question. There is a lot of subtlety here – especially in the fact that the question has never been randomized and that every group has its own indications for the use of CRT. While CRT can probably be removed for the majority of patients the numbers do not seem big enough to remove it in CNS3 patients or high-risk T-ALL patients.

Pregnancy and the Risk of Relapse in Patients Diagnosed with Hodgkin Lymphoma

Weibull, CE, (2016) Journal of Clinical Oncology (Link to abstract)

There is data from the 1950's to suggest that relapse might be more frequent in women who get pregnant after treatment for Hodgkin Disease. This is a retrospective study using the Swedish healthcare registry. Adult women with Hodgkin's Disease were followed for relapse and pregnancy. Pregnancy-related relapse was defined as relapse during or within 5 years of pregnancy. They found fewer pregnancy-associated relapses than predicted thereby providing no evidence that pregnancy is a risk factor for relapse of Hodgkin's Disease.

❖ Being a registry-based study, there are weaknesses including the fact that some pregnancies may not have been recorded if they occurred out of country or if there was no in-hospital care. However, this study is pretty decent evidence that clinicians should not advise against pregnancy for fear of relapse of Hodgkin Disease.

Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404

Barbara L. Asselin, (2016) JCO, (Link to Abstract)

Dexrazoxane was shown to have some cardioprotective effect if administered with anthracyclines. Some studies have reported a lower anti-tumour effect if administered with chemotherapies and a higher incidence of secondary malignancies. The purpose of this study was to determine the oncologic efficacy, cardioprotective effectiveness, and safety of dexrazoxane added to chemotherapy that included a cumulative doxorubicin dose of 360 mg/m2 to treat children and adolescents with newly diagnosed T-cell acute lymphoblastic leukemia (T-ALL) or lymphoblastic lymphoma.

537 patients were randomly assigned to either receive or not receive dexrazoxane. The 5-year event-free survival did not differ between groups.

Of 11 second malignancies, eight occurred in patients who received dexrazoxane (P = .17). The mean left ventricular fractional shortening, wall thickness, and thickness-to-dimension ratio z scores measured 3 years after diagnosis were worse in the doxorubicin-alone group (n = 55 per group; P=0.01 for all comparisons). Mean fractional shortening z scores measured 3.5 to 6.4 years after diagnosis remained diminished and were lower in the 21 patients who received doxorubicin alone than in the 31 patients who received dexrazoxane (22.03 v 20.24; P value 0.001)

❖ There is improvement in echocardiographic markers of heart function in patients receiving dexrazoxane without evidence of a clearly increased risk of secondary malignancy or worsened efficacy of treatment. There was, however, a non-significant trend towards increased secondary malignancies. Therefore weighing risk and benefit of dexrazoxane remains important but difficult.

Preclinical targeting of human T-cell malignancies using CD4-specific chimeric antigen receptor (CAR)-engineered T cells.

Pinez K, (2016) Leukemia (Link to Abstract)

Currently most clinical trials of CAR T-cells are against B-cell malignancies. There are not many studies about CAR T-cells against T-cell malignancies. In this paper, the authors described a CD4 antigen targeted CAR T-cell, derived from CD8+ T cells. They demonstrated the in vitro efficacy against CD4+lymphoma, leukemia cell lines and mouse models.

❖ CD4 CAR T cells present a new approach for the treatment of CD4+ T-cell malignancies. Although CD4 T-cell depletion leads to susceptibility of infection (as in HIV patients), this may potentially be used as a bridging therapy for bone marrow transplant.

Genome-Wide Profiles of Extra-cranial Malignant Rhabdoid Tumors Reveal Heterogeneity and Dysregulated Developmental Pathways

Chun, HJE, (2016) Cancer Cell (Link to abstract)

This study analyzes genomes, transcriptomes, DNA methylation, histone signatures, and microRNA in extracranial rhabdoid tumors. There are many different findings reported in this paper but in their totality they are evidence that rhabdoid tumors have heterogeneous molecular features despite all being initially driven by SMARCB1 mutations. Different techniques reveal slightly different subgroups but it is likely that there are two major groups of rhabdoid tumors – each seems to arise from a different neural crest cell precursor.

❖ When compared with similar studies in AT/RT – a very similar tumor, this study doesn't appear to reveal as many clinically-relevant findings. However, this is the first comprehensive analysis of rhabdoid tumor molecular features and is therefore an important starting point for treating these very difficult tumors.

Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction with Palliative Radiotherapy for Cancer-Induced Bone Pain

Fallon, M, (2016) Journal of Clinical Oncology (Link to abstract)

Pregabalin is a Calcium-channel blocker which is used for neuropathic pain treatment. This RCT in adults compared pregabalin vs placebo in the treatment of bone pain. Patients were also allowed to receive palliative radiotherapy. All patients were adults and most had breast, lung, or prostate cancer. All patients had at least 4/10 bone pain at the time of enrollment. A total of 233 patients were randomly allocated and although there were withdrawals in each arm, an intention-to-treat analysis was used. There was no difference between the groups in time to decreased pain scores, lower pain overall, lower opioid requirement, or in functional ability.

❖ This is a well designed trial that strongly argues against using pregabalin to treat pain related to bone metastases. It is mostly in adult patients with carcinoma but unless there is a model showing that the pathophysiology of cancer bone pain is different in sarcomas, embryonal tumors, or hematological malignancies there is not a strong argument to redo this expensive trial in children nor to use pregabalin for this indication.

Exploitation of the Apoptosis-Primed State of *MYCN*-Amplified Neuroblastoma to Develop a Potent and Specific Targeted Therapy Combination

Ham, J, (2016) Cancer Cell (Link to abstract)

This group used a drug screen to identify two molecules (ABT-263 and ABT-199) that inhibit growth in *MYCN*-amplified neuroblastoma cell lines. Through several lines of evidence, they show that *MYCN* amplification makes cells more prone to apoptosis and that apoptosis can be triggered by inhibiting BCL-2 as these molecules do. They then show that the degree of apoptosis is even greater when these molecules are combined with alisertib (an Aurora Kinase inhibitor) which seems to further reduce the apoptosis threshold in these cells. They finally show that the combination of these drugs induces sustained remission in xenograft mouse models. None of these effects are seen in wild type *MYCN* neuroblastoma.

❖ This is the first study to show quite conclusively that *MYCN* can be targeted with clinically available drugs. Alisertib has already been tested in phase I/II studies in neuroblastoma alone and in combination with irinotecan/ temozolamide; the barriers to testing this combination in humans will be lower than usual. As always, a mouse xenograft is not the same as a spontaneous arising human tumor so we should still maintain a level of skepticism in the face of these optimistic results.

Assessment of Primary Site Response in Children With High-Risk Neuroblastoma: An International Multicenter Study

Bagatell, R (2016) JCO (Link to Abstract)

Staging in neuroblastoma has transitioned from INSS which is a pathological system to INRGSS which is based on CT and MRI imaging. The purpose of this study was to look at the best way to evaluate tumor response comparing serial measurements of 3 dimensions of lesions to calculate volume, to one dimension of the lesions as per Response Evaluation Criteria in Solid Tumors (RECIST). Response of ≥30% reduction in longest diameter was used for RECIST, ≥50% reduction in volume as per INRC or ≥60% reduction in volume (because 30% reduction in diameter corresponds to 60% reduction in volume of sphere).

Data from 229 children with high-risk neuroblastoma from 7 centers were analyzed. Sensitivity to detect response in survivors was higher for volume response measures than single measure but there was low specificity of all response evaluations (to detect poor response in those who died). None of the response measures predicted outcome or extent of resection.

❖ Volume or single diameter response measurements on imaging does not predict survival in high-risk neuroblastoma, but still remains important to monitor for progression and overall response to treatment. As it is more complex to do 3-dimension measurements, and there was no difference in outcome prediction, the revised International Neuroblastoma Response criteria will use RECIST criteria using longest diameter going forward in future studies.

Prospective Study of ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites

Sadowski, S (2016) JCO (Link to Abstract)

^{68}Ga-DOTA-TATE PET/CT can be used to image tumors that express somatostatin including neuro-endocrine tumors (NET) and neuroblastoma. This was a prospective cohort study in adults to assess the utility of ^{68}Ga-DOTA-TATE PET/CT to diagnose and stage Gastro-entero-pancreatic (GEP) NET compared to current approved imaging modalities (^{111}In-pentetreotide SPECT/CT) and/or MRI.

131 patients with biochemically or radiologically suspected or proven GEP NETs underwent imaging: ^{68}Ga-DOTA-TATE PET/CT detected 95% lesions (45% MRI and 31% ^{111}In-pentetreotide SPECT/CT). They compared surgical specimens with imaging techniques and ^{68}Ga-DOTA-TATE PET/CT correctly found primary, Lymph node, and distant metastases in 64% compared to 22%, and 38%, respectively, with other imaging modalities). With additional findings from the imaging, clinical management was changed in a third of cases. In patients with symptoms of carcinoid syndrome, negative serum chromogranin A and urinary 5-HIAA levels, ^{68}Ga-DOTA-TATE PET/CT also detected lesions in 65% of patients when the majority of these were not found on the other imaging techniques.

❖ ^{68}Ga-DOTA-TATE PET/CT is better than ^{111}In-pentetreotide SPECT/CT and anatomical imaging in detecting and staging Gastro-entero-pancreatic NET and may find lesions even if biochemical markers are absent. This study suggests ^{68}Ga-DOTA-TATE PET/CT should be used in initial management and follow-up of adults with NETs. There are only limited studies in children with NETs and also neuroblastoma ,which expressed Somatostatin receptors, and targeted therapy with ^{177}Lu-DOTA-TATE is being investigated.

AT/RTs are Comprised of Three Epigenetic Subgroups with Distinct Enhancer Landscapes

Johann, PD, (2016) Cancer Cell (Link to abstract)

This German group utilized DNA methylation and expression profiles to subtype AT/RTs into 3 separate subgroups – tyrisonase (TYR), sonic hedgehog (SHH), and MYC. These 3 subgroups are characterized by the active pathways in them as well as by the location of enhancers and the relative importance of different transcription factors. The finding of different activated elements in tumors that are generally mutationally quiet (other than *SMARCB1)* mutations may allow for more targeted therapies which the authors start to show with in-vitro apoptosis achieved using a MITF inhibitor in the TYR group.

❖ This study is part of the worldwide (unfortunately uncoordinated) effort to subgroup embryonal tumors in a manner parallel to the successful medulloblastoma classification. While this study seems convincing, it is not consistent with another study (Torchia et al., Lancet Oncology 2015) showing only 2 subgroups of AT/RT with different features. The degree of overlap between these two classification systems is yet to be seen.

Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study.

Jakacki, R, (2016) Neuro-Oncology, (Link to Abstract)

Authors report results of COG ACNS0423, a phase 2 study evaluating efficacy of temozolomide and lomustine combination in maintenance therapy in childhood high-grade glioma. Results are retrospectively compared to previous study ACNS0126 where temozolomide only was used. In the current study, it was shown that combination temozolomide and lomustine in 108 patients improves 3-year EFS to 22% (compared to 11% in ACNS0126). On the other hand this treatment was accompanied by significant hematological toxicity requiring dose reductions in 68% patients.

❖ The addition of lomustine to temozolomide as adjuvant therapy in ACNS0423 was associated with significantly improved outcome compared with the preceding COG ACNS0126 HGG study in which participants received temozolomide alone.

REVIEWS/ PERSPECTIVES

Targeting EZH2 in cancer.

Kim, K, (2016), Nature medicine, (Link to abstract)

This is a review of EZH2 (enhancer of zeste homolog 2) which has important roles in many cancers e.g. NHL (where it is mutated) and in many others where it is overexpressed e.g. ovarian, melanoma, T-ALL. EZH2 is discussed as a therapeutic target and EZH2 inhibitors in development are reviewed.

Section 4. Supportive Care, Survivorship, General Pediatrics & other updates

Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study

Henderson, TO, (2016) Journal of Clinical Oncology (Link to abstract)

Another study delves into the Childhood Cancer Survivors Study (CCSS) cohort and uses their big numbers to find a small signal. In particular, female survivors are at a higher risk of breast cancer at a young age than their siblings even when they receive no radiotherapy. Although the standardized incidence ratio (similar to relative risk) is high at 4.0 compared to the general population, the absolute risk by age 45 is 1.2% in survivors. The biggest risk factors for developing breast cancer were initial diagnosis of ALL or sarcoma and higher doses of alkylators or anthracyclines.

❖ This study should make us think about how we follow up our survivors. The findings seem to draw attention to high doses of anthracyclines and alkylators as risk factors and this is physiologically plausible. However, breast cancer at a young age is a criterion for Li Fraumeni syndrome and since sarcoma and hypodiploid ALL are also part of this disease it needs to be considered as a possible explanation. It's also important to bear in mind that sarcoma patients get some of the highest doses of anthracyclines and alkylators introducing a confounder.

Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure

Richardson PG, (2016) Blood, (Link to Abstract))

Veno-occlusive disease is a well-known complication of HSCT with a high mortality in patients developing multi organ failure of >80%. The authors assessed 102 patients with a diagnosis of veno-occlusive disease (VOD) and multi-organ failure. These patients were given defibrotide 25mg/kg/d and were compared to 32 historical controls. Survival at +100 days was 38.2% in the defibrotide group vs. 25% in controls (p=0.01). Day +100 complete response was seen in 25.5% in the treatment group vs. 12.5% in controls. Adverse events were encountered in a similar incidence in the two groups. Day +180 survival was not statistically significant but the authors point out that the causes of death were not directly related to VOD.

❖ Defibrotide 25mg/kg/d in patients with multi-organ failure was safe and survival was improved at +100 days but not at +180 days. In conclusion, defibrotide can be given in multi-organ failure due to VOD but long-term survival benefits were not shown.

REVIEWS/ PERSPECTIVES

Looking Back to Inform the Future: Lesson Learned From Survivors of Childhood Cancer.

Armenian S, (2016), Cancer, (Link to Abstract))

An editorial discussing childhood cancer – a little history and survivorship goals.
