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BestBits of the Pediatric Hematology Oncology literature

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Introduction

BestBits of the Literature 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 hematology and oncology. Short summaries are presented with the reviewer's conclusion on the impact of the findings. All articles are posted on bestbits.ca.

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Section 1. General Hematology, Thrombosis & Transfusion Medicine

Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults

Cooper, DJ et al, 2017, New England Journal of Medicine

Packed red cells stored over time tend to develop a series of biochemical changes known as a "storage lesion". Clinicians have long been concerned that these storage lesions have an effect on outcomes for patients receiving transfusions. Although two previous RCTs have shown that this is not true, criticisms were levelled against each. Specifically, the INFORM trial had a low overall mortality potentially reducing its power while the ABLE trial evaluated only transfusions given soon after ICU admission. This multicenter RCT (TRANSFUSE) aimed to address these issues.

Nearly 5000 adults admitted to ICUs in 5 countries and receiving red cell transfusions were randomized to the freshest blood product available or the oldest blood product available. The primary outcome was 90-day mortality with a number of other secondary outcomes. Randomization was computerized and patients, caregivers, and research personnel were blinded to treatment allocation.

There was no overall difference in mortality between the two groups (24.1% vs 24.8%). A pre-specified subgroup analysis showed a higher mortality in patients with high APACHE III scores (higher risk of ICU death) receiving fresh red cells and a lower mortality in patients with low APACHE III scores receiving fresh red cells. Other subgroup analyses (blood group, SOFA score) and secondary outcomes had no difference between treatment allocations other than a slightly higher non-hemolytic febrile transfusion reaction rate in the fresh pRBC group.

Several exclusion criteria limit generalizability. One exclusion criteria was physician preference to give a particular blood product which may have subtly biased the results. No children were included and all these patients were critically ill.

❖ Overall, a large and important study once again indicating that the age of red blood cells should not be a major factor in the clinical decision making around transfusions.

How I manage children with neutropenia

Dale, DC, 2017, British Journal of Haematology

❖ This is a review on the management of children with neutropenia with a special emphasis on clinical finding, laboratory tests, and treatment, particularly the use of granulocyte colony-stimulating factor.

Frequency and epitope specificity of anti-factor VIII C1 domain antibodies in acquired and congenital hemophilia A

Kahle, J et al, 2017, Blood

Inhibitor development is the most challenging treatment-related complication in congenital Hemophilia, and autoantibody development in adults is associated with the equally challenging acquired Hemophilia A. Earlier studies suggested that the majority of both allo- and auto-antibodies were directed against the A2 and C2 domains of Factor VIII (F.VIII), with the autoantibody more likely to be restricted to a particular domain. Recently, inhibitors developing in a patient with mild Hemophilia A were found to target the C1 domain. Subsequent studies identified anti-C1 antibodies in up to 60% of inhibitors, and the response was greater to human than porcine F.VIII.

This study analyzed the frequency and epitope specificity of anti-C1 antibodies in patients with both acquired and congenital hemophilia.178 patients (63 congenital, 115 acquired) were studied by a variety of protein based and molecular

methods. Human and porcine protein sources were studied in tandem, primarily because of the potential role of porcine replacement factor in patients with inhibitors and those with acquired hemophilia A.

The median inhibitor titre of the population was 5.4 BU (ranging from 1.9-20). C1-specific antibodies were found to contribute significantly to the total population of cross-reactive (human and porcine sequence) anti-F.VIII IgG. The C1 domain was noted to be important in binding to phospholipid membranes, F.V, and von Willebrand Factor, which could explain its impact in coagulation. As a primary in vitro study, it is difficult to determine the true in vivo impact of these antibodies, or to compare them to the effects of antibodies against other epitopes. Some patients may also have antibodies to multiple epitopes, particularly in congenital hemophilia, with a more complex impact on coagulation and treatment.

❖ Recent studies are highlighting both treatment and patient-related risk factors for inhibitor development. Given the clinical importance of inhibitor development, a better understanding of the nature and variability of inhibitors should contribute to the ability to better prevent and eradicate them with new approaches.

Indications for and Adverse Effects of Red-Cell Transfusion

Carson, JL et al, 2017, New England Journal of Medicine

❖ A helpful review of red cell transfusions encompassing evidence underlying current transfusion guidelines, trends in use, the infectious and non-infectious risks of transfusion, ongoing research, and effects in children.

Minimal Factor XIII activity level to prevent major spontaneous bleeds

Menegatti et al, 2017, Journal of Thrombosis and Haemostasis

Factor XIII deficiency is a rare but serious bleeding disorder. This study aimed to validate a bleeding severity classification, and to identify the minimal FXIII level at which patients remain asymptomatic, in order to guide factor prophylaxis.

This was an international multi-center cross-sectional study. 64 patients from 12 countries were identified as part of the European Prospective Rare Bleeding Disorders Database (PRO-RBDD). A previous retrospective study had suggested the following bleeding severity classification: severe (undetectable FXIII), moderate (0-29 U/dl), and mild (>30 U/dl). The patients were analyzed according to this classification in order to validate it. FXIII levels were tested using the ammonia release assay and centralized testing was attempted. Bleeding severity was classified as follows: Grade 1 (asymptomatic), Grade 2 (spontaneous minor - mucocutaneous), Grade 3 (spontaneous major - umbilical, GI, CNS, hemarthrosis, hematoma).

FXIII level correlated with bleeding severity, with 90% of patients with severe FXIII deficiency exhibiting Gr.3 bleeding, as compared to 46% of moderate, and 0% of mild patients. Conversely, 43% of mild patients were asymptomatic. Unsurprisingly, patients with severe FXIII deficiency presented at a younger age (median 0 years) and were most likely to be symptomatic. All patients suffering from Gr.3 bleeding had a FXIII level under 16 U/dl. Thus, using a cut-off of 15 U/dl was predicted to have a sensitivity of 97% and specificity of 76% in discriminating between patients at risk of having Gr.3 bleeds.

Limitations include a study population that is skewed towards symptomatic patients as the majority of patients were identified by presenting to the hospital with bleeding. In addition, less than half of the samples were sent to the central laboratory to confirm FXIII level, though there was high concordance in the samples that were sent. Strengths include a relatively large sample size for a rare disorder, and a heterogeneous group of patients from multiple countries. Moreover, as the population will be studied prospectively there is an opportunity to test the validity of the cut-off of 15 U/dl as a trough level for prophylaxis.

❖ The severity classification accurately categorizes patients in bleeding phenotype. A FXIII level below 15 U/dl greatly increases the likelihood of spontaneous major bleeding. As such, the use of 15 U/dl as a trough target level for prophylaxis is reasonable.

Long-term safety and efficacy of deferasirox in young pediatric patients with transfusional hemosiderosis: Results from a 5-year observational study (ENTRUST)

Vichinsky, E et al, 2017, Pediatric Blood and Cancer

The oral, once-daily iron chelator deferasirox is indicated for the treatment of adult and pediatric patients with chronic iron overload. However, fewer than 10% of patients in the registration studies were aged 2 to less than 6 years. Therefore, further collection of efficacy and safety data in young patients was necessary.

This observational 5-year ENTRUST study enrolled patients aged 2 to less than 6 years with transfusional hemosiderosis. They received deferasirox according to local prescribing information. The primary objective was the evaluation of safety, specifically renal (serum creatinine) and hepatic (ALT) function. Serum ferritin was also observed as a surrogate efficacy parameter.

267 patients were enrolled. Mean age was 3.2 years. The most frequent diagnosis was β-thalassemia. 145 patients (54.3%) completed 5 years' treatment. The proportion of patients with two or more consecutive post-baseline measurements (≥7 days apart) of serum creatinine higher than age-adjusted upper limit of normal (ULN) and ALT more than five times the ULN was 4.4% and 4.0%, respectively. Median serum ferritin decreased from 1,702 ng/ml at baseline to 1,127 ng/ml at 5 years. No new or unexpected safety findings were observed with regard to adverse effects or laboratory abnormalities, with a limited number of patient discontinuations as a direct result of adverse effects.

Almost half of enrolled patients discontinued the study before the end. This is a considerable proportion of the patients enrolled. Even if the main reason of discontinuation was not adverse effects (only 6,7%), it is possible that this high proportion of discontinuations introduced some biases. Also, because this study was observational without predefined therapy protocol, it did not determine if more aggressive therapy could result in a higher incidence of AEs. Finally, this study was funded by Novartis and some of the authors reported consultancy and some research funding from Novartis.

❖ This study provides real-world evidence that supports the manageable safety profile and sustained efficacy of long-term deferasirox therapy in pediatric patients aged 2 to less than 6 years at enrollment with transfusional hemosiderosis.

Section 2. Leukemia and Lymphoma & Bone Marrow Transplantation

Autologous hematopoietic stem cell transplantation for pediatric multiple sclerosis: a registry-based study of the Autoimmune Diseases Working Party (ADWP) and Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplant

Burman, J et al, 2017, Bone Marrow Transplantation

Approximately 5% of multiple sclerosis (MS) patients are diagnosed before 18 years. Pediatric onset is associated with an earlier disability than patients with adult onset and cognitive impairment is present in about 30%. Disease-modifying drugs are available but a relapsing course is frequent. While autologous hematopoietic stem cell transplantation (HSCT) has been investigated for decades in adults with promising results, there are only very few pediatric patients reported in the literature.

The retrospective multicenter study analyzed data from the European Bone Marrow Registry and identified 22 patients from 7 centers. Additional information was requested from the identified centers by questionnaires. Data was available for 21 patients, who were included in the study. All patients had been treated with disease-modifying treatments prior to HSCT, 11 with more than one. 20 patients received anti-thymocyte globulin as part of their conditioning regimen. 18 patients had follow-up data available, 2 patients experienced clinical and MR-radiological relapse about two years after HSCT. Another patient was identified as having subclinical disease with enhancing lesions on MRI. 16 patients improved in their disability scores. All patients were alive at last follow-up and only one patient experienced serious HSCT-related complications (sepsis with ICU admission).

This study is limited as a small retrospective study. Follow-up data was not available for all and the median follow-up duration was only 2.8 years. There was no comparison group to relate the outcome after HSCT to a reference group of pediatric MS patients.

❖ Autologous HSCT can be considered as a treatment option in pediatric-onset multiple sclerosis patients where first-line treatment was not effective. However, long-term outcome data are missing and therefore this treatment option still must be considered experimental.

Tregs: hype or hope for allogeneic hematopoietic stem cell transplantation?

Lussana, F et al, 2017, Bone Marrow Transplantation

❖ This review on regulatory T cells summarizes current concepts and knowledge on their effect in allogeneic stem cell transplantation, particularly in the treatment and prevention of graft versus host disease.

CD33 Splicing Polymorphism Determines Gemtuzumab Ozogamicin Response in De Novo Acute Myeloid Leukemia: Report from Randomized Phase III Children's Oncology Group Trial AAML0531

Lamba, JK et al, 2017, Journal of Clinical Oncology

Gemtuzumab ozogamicin (GO) is a monoclonal antibody targeted against CD33 with known activity in AML. GO was studied in conjunction with standard five-course chemotherapy in the COG AAML0531 trial. A small pilot study indicated that there is an association between a SNP in CD33 (rs12459419) and the patient's response to GO. Specifically, CT and TT SNP genotypes are associated with a loss of exon 2, which contains the GO binding region, while the CC genotype preserves this binding region. The purpose of this study was to quantify the impact of this in patients with AML treated with GO and standard chemotherapy as part of AAML0531.

The COG AAML0531 trial enrolled patients with AML and randomized them to receive either a standard five-course chemotherapy or chemotherapy with the addition of two doses of GO (N=816; 50% received GO). Genotype at the CD33 SNP were determined at diagnosis for all patients.

Of the 816 patients, 415 had the CC genotype, 316 (39%) had the CT genotype and 85 (10%) had the TT genotype. There was no difference in genotype frequency by sex, treatment arm, disease characteristics or receipt of HSCT during treatment; however, there was a significantly higher rate of the SNP in white patients than in black patients (P=0.001). Patients with the CC genotype had a significantly lower relapse risk in the GO arm of the trial compared to the No-GO arm (26% vs 49%; P=0.001), and higher disease-free survival (65% vs 46%; P=0.004). There was no difference found for the patients with CT or TT genotypes between the two treatment arms for either relapse rate or disease-free survival.

The limitations of this study include the incomplete understanding of the CD33 rs12459419 mechanism of action. Given the complexity of the effects of various promoter regions and other molecular factors, it is important to fully elucidate these mechanisms to understand the implications of the SNP better.

❖ Gemtuzumab Ozogamicin appears to significantly decrease relapse rates and increase disease-free survival in children with AML who also have the CC genotype of the SNP rs12459419. There was also a higher rate of CD33 SNP seen in white patients. This study raises the question of whether we should target therapy to genotype in AML.

Neurocognitive Functioning of Children Treated for High-Risk B-Acute Lymphoblastic Leukemia Randomly Assigned to Different Methotrexate and Corticosteroid Treatment Strategies: A Report from the Children's Oncology Group

Hardy, KK et al, 2017, Journal of Clinical Oncology

Survivors of childhood ALL are at increased risk for a number of late effects due to treatment, individual and environmental factors, including neurocognitive deficits. This study examined whether there was a difference in neurocognitive outcomes based on the treatment administered during a COG protocol for high-risk B-ALL, with the goal of being able to identify those at increased risk to facilitate earlier intervention. Specifically, this study examined the effect of steroid choice and dosage and method of methotrexate administration on intellectual functioning, working memory and processing speed via a randomized control trial.

192 children who had been enrolled on the COG protocol AALL0232 were examined for IQ, working memory and processing speed 8-24 months after the completion of their HR B-ALL therapy. The children had been randomly assigned, during the initial AALL0232 protocol, to receive either prednisone or dexamethasone (during induction), and to receive either four courses of high dose methotrexate with leucovorin rescue or five doses of escalating dose methotrexate (Capizzi) with PEG asparaginase (during interim maintenance).

After controlling for age, gender, race, ethnicity, time since diagnosis and type of medical insurance, there was no significant difference in IQ, working memory or processing speed found 8-24 months post completion of therapy comparing the different treatment groups. However, both, age and type of medical insurance were found to be significant predictors of decreased IQ (P 0.001), age was also found to be associated with decreased processing speed (P = 0.02) and insurance type (public health insurance rather than private or military insurance) with decreased working memory (P 0.001).

Limitations of this study included its small size, as less than 20% of eligible subjects participated, and the generally younger age and less ethnic diversity of patients captured in this trial. The cross-sectional design is also a limitation, as it would be more useful to measure neurocognitive function longitudinally over time. Finally, there are limitations inherent in the tests used to estimate neurocognitive function.

❖ No association between increased neurocognitive late effects and choice of steroid and type of methotrexate administration was found in children who received treatment for high-risk B-ALL; however, there was an increased risk of neurocognitive dysfunction in younger children, and those from a lower socioeconomic status (estimated by type of medical insurance coverage), who might benefit from earlier neurocognitive interventions.

Neurocognitive outcomes among children who experienced seizures during treatment for acute lymphoblastic leukemia

Nassar, SL et al, 2017, Pediatric Blood & Cancer

This article describes the incidence, risk factors, and neurocognitive outcomes for treatment-related seizures among children undergoing treatment for ALL and registered on the St. Jude Total Therapy XV protocol at three time points. This study omitted craniospinal radiation for all treatment groups. Patients with low-risk ALL received triple intrathecal therapy. This was a retrospective review of this patient cohort. Prospective neuropsychological assessments and MRIs were planned for all patients treated on this protocol (498 patients). Each patient with treatment-related seizure was matched with two cohort patients who did not develop seizures.

Nineteen patients developed seizure (2-year cumulative risk of 3.82 ± 0.86% standard error) and 2 had a prior history of seizures. No risk factors for developing seizures were identified. The intensive chemotherapy on the standard/high-risk arm compared to the low-risk arm may be associated with seizure development but not found to be statistically significant. Problems with attention, working memory, and processing speed were more common in the seizure group. Cognitive deficits persisted 2 years after therapy. Increased rates of leukoencephalopathy on MRI were detected in the seizure group.

An important limitation is the retrospective design. The initial neuropsychological assessment was performed after a dose of high-dose methotrexate, which may not represent a true baseline.

❖ Seizure development during treatment for ALL was found to be associated with neuropsychological changes, even at 2 years post treatment. There may be an association with more intensive therapy. These outcomes should be incorporated in a prospective treatment protocol. This study raises the question whether children who experienced seizures during therapy should be followed more closely by neuropsychology.

Pretransplant Vitamin D Deficiency Is Associated With Higher Relapse Rates in Patients Allografted for Myeloid Malignancies

Radujkovic, et al, 2017, Journal of Clinical Oncology

Vitamin D has been shown to affect multiple signalling pathways and immune responses. It has been identified that Vitamin D deficiency is common in patients with hematologic malignancy. This is a retrospective cohort study to evaluate the impact of pre-transplant Vitamin D status on outcomes.

Patients undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT) for myeloid and lymphoid malignancies between 2002-2013 at one centre formed the training cohort. The following data was collected: OS, relapse, NRM, disease stage, conditioning, patient age, donor type, recipient/donor sex match, GVHD information. Vitamin D deficiency was defined as 25-hydroxyvitamin D320ng/mL. Validation was performed in a cohort of patients with alloHSCT for AML/MDS between 2009-2013 at different centres (independent cohort).

In the training cohort, 492 patients (age range 17 -75) were assessed and 80% Had Vitamin D deficiency before alloHSCT. Vitamin D deficiency was significantly associated with a higher risk of relapse and inferior overall survival. For ALL, Vitamin D deficiency was associated with significantly inferior OS. For AML, pre-transplant Vitamin D deficiency was only significantly associated with higher risk of relapse. A higher relapse risk was also observed in myeloid diseases in the independent patient cohort.

Retrospective study with risk of confounding bias, such as information about treatment prior to HSCT including length of stay in hospital, infections, complications. Adult study and therefore not directly transferrable to pediatrics. The independent cohort only included patients with AML, thus ALL findings not validated in separate cohort. There was no data providing insight on possible mechanisms leading to the effect on outcome.

❖ In adult patients with hematologic malignancies, Vitamin D deficiency seems to be associated with worse outcomes (OS and/or relapse). Due to minimal risk, vitamin D supplementation seems reasonable to try and prevent deficiency in all patients that will need allo-HSCT.

Arsenic Consolidation Allows Anthracycline Dose Reduction for Pediatric Patients with Acute Promyelocytic Leukemia: Report from the COG Phase III Historical Controlled trial AAML0631

Kutney, MA et al, 2017, Journal of Clinical Oncology

APL0406 demonstrated that all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) were not inferior in adults with acute promyelocytic leukemia (APL). This study reduced anthracyclines by 40% (to decrease risk of cardiotoxicity) and incorporated ATO in treatment for pediatric APL. The aim of this study was to demonstrate safety and tolerability of ATO in consolidation in pediatric patients and maintain same outcomes.

Nonrandomized, multicentre, phase III trial compared to historical data: AIDA 0493: 2-22 years old, de novo APL [t(15:17) confirmed by PML-RARα PCR]. The treatment protocol similar to AIDA 0493 except ATO 0.15mg/kg/d added to consolidation and cumulative daunorubicin equivalent reduction to 335mg/m2 for standard risk and 385mg/m2 for high-risk instead of 600mg/m2. Designed to detect an 11% decrease in EFS for SR patients.

Patients were enrolled from March 2009 - November 2012, 101 patients were evaluated. 3-year OS was 94% (SR 98%, HR 86%), 3-year EFS was 91% (SR 95%, HR 83%). AAML0631 was non-inferior to previous study. Events in this trial included 3 relapses, 2 second malignancies, and 7 deaths. Cardiac toxicities during ATO: 16% new grade 1 QTc prolongation, 12% grade 2 QTc prolongation, 1 patient grade 3 QTC prolongation, 1 patient grade 1 ventricular arrhythmia, 1 patient left ventricular dysfunction. Off therapy 1 patient grade 1 QTc prolongation, 1 patient grade 2 ventricular arrhythmia. There were no cardiac deaths and minimal liver toxicity. This is a historical comparison with AIDA 0493 which enrolled patients between 1993-2000 and only descriptively described HR patients in this study.

❖ Addition of ATO and reduction of anthracyclines in AAML0631 seems to be non-inferior when compared to historical control and minimal adverse events, including cardiac toxicities.

Central nervous system involvement in acute lymphoblastic leukemia is mediated by vascular endothelial growth factor

Munch, V et al, 2017, Blood

Treatment of the central nervous system in acute lymphoblastic leukemia is critical, even in the absence of detectable involvement at diagnosis. This suggests subclinical involvement in many ALL patients at diagnosis. Multiple factors have been evaluated in relation to CNS involvement, which is described as leptomeningeal disease. This study identified vascular endothelial growth factor A (VEGF) as a mediator of CNS involvement of ALL.

The study used the immunodeficient NOD/SCID mouse model to investigate key molecular features of CNS disease in ALL, as a model to study leukemia-cell entry into the CNS. Patient ALL cells were successfully transplanted into these mice, and hematopoietic stem cell and meningeal cell suspensions were evaluated after autopsy. An in vivo component of the study saw mice assigned to receive bevacizumab, an inhibitor of VEGF, or placebo.

Overt leukemia was seen in all transplanted mice, and 9 of 15 developed CNS symptoms. The CNS+ phenotype was maintained with subsequent transplantations, indicating that CNS involvement is intrinsic to the ALL cell. CNS+ ALL was identified as having increased expression of VEGF, which regulates vascular permeability and transendothelial migration in addition to angiogenesis. The overall growth and proliferation of the ALL cells was not affected by VEGF capture in vitro by bevacizumab, but transendothelial ALL cell migration was decreased. This was replicated in vivo, with a clear reduction in CNS leukemia seen in the bevacizumab treated mice, although no reduction in their leukemia was observed. While 9 mice developed CNS leukemia, this did not correspond to the patients from whom the xenografts were derived. As such, it is difficult to extrapolate completely from the mouse model to the human disease.

❖ ALL cell entry to the CNS is intrinsic to the leukemia, and associated with increased expression of VEGF. Bevacizumab, a VEGF inhibitor, may provide a novel therapeutic strategy to control CNS leukemia.

Outcome of children with acute leukemia given HLA-haploidentical HSCT after ab T-cell and B-cell depletion

Locatelli, F et al, 2017, Blood

Haploidentical hematopoietic stem cell transplantation (HSCT) is an option for transplantation in patients without a suitable matched donor. CD34+ positive selection is traditionally used to prevent both graft failure and severe graft-versus-host disease (GVHD), but is associated with prolonged lymphopenia and delayed immune reconstitution. Selective depletion of (alpha-beta) T lymphocytes and B cells from a haploidentical donor allows transplantation of both donor hematopoietic stem cells and also committed progenitor cells, NK cells, and (gamma-delta) T lymphocytes to improve post-transplant immune reconstitution and decrease life-threatening infections.

In this prospective trial, children with acute lymphoblastic or myelogenous leukemia without an available matched sibling or unrelated donor were offered a selectively cytoreduced haploidentical transplant. All patients received myeloablative conditioning, anti-T lymphocyte globulin for GVHD prophylaxis and conditioning, and Rituximab for EBV-related PTLD prophylaxis. This cohort was compared to children receiving either a matched sibling or matched unrelated transplant in the same period at the centre.

80 children were enrolled in the cohort; two failed to engraft. No serious acute GVHD occurred, and the overall incidence of limited chronic GVHD was only 5%. Four patients died of treatment-related causes, for a 5-year cumulative incidence of 5%. 19 patients (24%) have relapsed, with 15 in the first year after transplantation; only use of total body irradiation had a significant impact on relapse rate in multivariate analysis. 5-year overall survival was 72%, and this group was comparable to the compared matched sibling and unrelated groups.

Novel approaches such as post-transplantation cyclophosphamide were not evaluated in this regimen, which might allow for decreased intensity of conditioning. Rituximab prophylaxis may have contributed to the low incidence and severity of acute GVHD through recipient B-cell depletion. This was a single-centre trial of a highly specialised graft-manipulation, less experienced centers might not be able to achieve the same quality of graft manipulation.

❖ Even in the absence of post-transplantation pharmacological prophylaxis, patients receiving a selectively (alpha-beta) T-cell and B-cell depleted haploidentical HSC had both a high engraftment rate and a low incidence of GVHD. This type of transplantation offers comparable risks of treatment-related morbidity and mortality and relapse for patients who would otherwise lack a suitable donor.

Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study

Wolthers, BO et al, 2017, Lancet Oncology

Asparaginase is an essential drug in the treatment of acute lymphoblastic leukemia, but is also associated with several toxicities, one of the most severe being asparaginase-associated pancreatitis. The aim of this study was to investigate the risk of complications and risk of re-exposing patients with a history of asparaginase-associated pancreatitis to further asparaginase therapy. Other outcomes were investigation of the diagnostic criteria for asparaginase-associated pancreatitis and differences in asparaginase-associated pancreatitis phenotype between patients receiving different types of asparaginase.

This is an observational study, where patient files from 26 trials run by 18 trial groups were reviewed on children diagnosed with t(9;22)-negative acute lymphoblastic leukemia, who within 50 days of asparaginase exposure developed asparaginase-associated pancreatitis.

In this study, 465 patients with asparaginase-associated pancreatitis were included: 26% developed pseudocysts, 21% needed acute insulin therapy, 8% needed mechanical ventilation, and 2% of 458 patients died. Risk of assisted mechanical ventilation, need for insulin, pseudocysts, or death was associated with older age, and having one or more affected vital signs (fever, hypotension, tachycardia, or tachypnoea). 1 year after diagnosis of asparaginase-associated pancreatitis, 11% still needed insulin or had recurrent abdominal pain or both, which were associated with having had a pseudocyst. 96

patients were re-exposed to asparaginase, including 59 after a severe asparaginase-associated pancreatitis. 46% patients developed a second asparaginase-associated pancreatitis.

The high frequency of affected vital signs at diagnosis of asparaginase-associated pancreatitis could be misdiagnosed as having sepsis. Grading of severity was misleading. No dose association or other medication that can cause pancreatitis were examined in this study.

❖ The risk of a second asparaginase-associated pancreatitis was not associated with severity of the first asparaginase-associated pancreatitis and having a second asparaginase-associated pancreatitis was not associated with risk of persisting complications, therefore re-exposure to asparaginase should be determined mainly by the anticipated need of asparaginase for antileukemic efficacy.

Section 3. Oncology: Solid Tumors and Neuro-Oncology

Identification of GPC2 as an Oncoprotein and Candidate Immunotherapeutic Target in High-Risk Neuroblastoma.

Bosse KR et al, 2017, Cancer Cell

This research aimed to find an immunotherapeutic target in neuroblastoma other than GD2 with low expression in normal tissue in order to develop new therapies that may be less toxic than dinituximab or to use in relapsed/refractory patients.

Publicly available RNA sequencing data from TARGET (high risk neuroblastoma) and GTeX (control) data were initially used. The group identified membrane-associated proteins highly expressed in neuroblastoma and not in normal tissues. Further studies were then done with the best target (GPC2) to validate its expression levels and to assess its role in neuroblastoma growth. Finally, an antibody-cytotoxic conjugate was developed and tested both in cell lines and in a patient-derived xenograft murine model.

GPC2 protein was found to be expressed on the membrane in most neuroblastoma cell lines, tumors, and patient-derived xenografts but at varying levels. It was expressed at lower levels in the esophagus and skin but the tumour-associated protein was a different isoform. Tumors with MYCN amplification and 7q gain had high GPC2 expression. The protein was found to be essential for growth and proliferation of cell lines as was expected as it has been previously shown to be a growth factor receptor. An antibody conjugate against GPC2 was effective both in cell lines and in a patient-derived xenograft murine model. Interestingly, GPC2 is also highly expressed in medulloblastomas and retinoblastomas.

The antibody-drug conjugate hasn't yet been tested in humans and the pharmacokinetics may be different from those in mice.

❖ Very nicely done study indicating a new therapeutic target in neuroblastoma (and potentially also in medulloblastoma and retinoblastoma). Furthermore, this RNA sequencing approach could potentially be used in other difficult tumours to develop immunotherapy.

Management of adrenal masses in patients with Beckwith–Wiedemann syndrome

MacFarland, SP et al, 2017, Pediatric Blood & Cancer

This study seeks to outline recommendations for managing incidental adrenal masses in children with Beckwith-Wiedemann syndrome (BWS). Adrenal findings from children followed at the Children's Hospital of Philadelphia were described.

Adrenal findings of patients in the institutional database were reviewed. A literature review and institutional experience were used to create the guidelines. The COG approach to subdividing age and size classification was used.

Most adrenal masses were detected incidentally on screening ultrasounds done to detect Wilms tumours or hepatoblastomas. 47 patients had adrenal masses - 3 neuroblastoma, 5 pheochromocytoma, 1 adrenocortical carcinoma. The proposed guidelines risk-stratify patients based on age and clinical features. Patients under 6 months and patients with cystic masses can be observed for size increase by ultrasound every 3 months. The evaluation of solid masses depends on MIBG and urine HVA/VMA results and hormone levels (random cortisol, ACTH, 17(OH) progesterone, DHEAS, androstenedione, testosterone).

The details of the literature review were not described so it is unclear if it was performed in a systematic way. These guidelines, though comprehensive, have not been validated prospectively. Many of the patients were not confirmed to have Beckwith Wiedemann Syndrome (hemihyperplasia by itself is not sufficient for diagnosis) and it is possible that there is a bias towards reporting more aggressive tumours such as neuroblastoma.

❖ This article proposes an approach to evaluating and managing adrenal masses in children with BWS based on age and high-risk features. It is unclear how the data in this paper is used to create these guidelines and so they are best thought of as expert opinion.

The clinical significance of equivocal findings on spinal MRI in children with medulloblastoma

Bennett, J et al, 2017, Pediatric Blood & Cancer

Children with medulloblastoma and spinal metastasis receive an increased dose of craniospinal irradiation (CSI). This article aimed to describe cases of equivocal abnormalities (nerve root clumping, linear vascular enhancement, nerve root enhancement and other vague findings) as they relate to prognosis. This is a single-centre, retrospective review.

Children ≥ 3 years of age diagnosed with medulloblastoma between 1988 and 2012 who were treated with upfront CSI were included. Blinded reviewers assessed the initial spinal MRI for equivocal findings.

100 patients were included, with equivocal findings in 48%. Most (94%) had MRI imaging preoperatively. A higher proportion of the sonic hedgehog (SHH) subgroup patients had equivocal findings (statistically significant). 5-year OS of children with equivocal findings did not differ from those with normal MRI findings (80 vs 84%).

Limitations of this study include retrospective nature and variety of treatment protocols across the time period, limiting comparison of survival outcomes. The imaging reviewers were not all radiologists although one radiologist reviewed each scan.

❖The presence of equivocal findings were not associated with worse OS compared to patients with normal MRIs, though the significance of the study results should be validated prospectively in the context of contemporary treatment protocols.

Therapeutic and Prognostic Implications of the BRAF V600E in Pediatric Low-Grade Gliomas

Lassaletta, A et al, 2017, Journal of Clinical Oncology

Pediatric low-grade gliomas (PLGGs) are a heterogeneous group of tumours. BRAF V600E-mutatant PLGGs are thought to represent a unique, more aggressive subtype, however this is controversial. BRAF V600E is a potentially targetable mutation.

Retrospective study. Genetic, clinical, treatment, and outcome data from an unselected group of patients with PLGGs from a single centre database (Toronto, n=405) compared to outcomes from an independent cohort of patients with BRAF V600E-mutated PLGG from 18 collaborating international pediatric centres (n= 180).

BRAF V600E mutation was detected in 17% patients with PLGG in the Toronto cohort and these patients had worse outcome compared to wild-type PLGGs with 10-year PFS 27% vs 60% and OS 84% vs 92%. PFS and OS were similar when compared to independent cohort outcomes. Multivariate analysis identified that patients with BRAF V600E mutation, CDKN2A deletion and incomplete resection had the worst prognosis. Six patients treated with BRAF inhibitor after progression with conventional therapy had significant response, median follow up 18.5 months.

Single centre study but compared outcomes to smaller international cohort which demonstrates similar outcomes. Too few patients from one centre to truly understand the role of BRAF inhibitors in this patient population.

❖ BRAF V600E PLGGs are unique group with worse disease course. May be beneficial to biopsy all LGGs to assist with treatment decisions.

Open-label, multicentre, randomised, phase II study of EpSSG and the ITCC evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue sarcoma (the BERNIE study)

Chisholm, JC et al, 2017, European Journal of Cancer

This paper reported on the results of a European pediatric Soft tissue sarcoma Group (EpSSG) and the European Innovative Therapies for Children with Cancer (ITCC) consortium. It was a multi-center, randomized phase II study that evaluated the addition of bevacizumab to standard chemotherapy in children and adolescents with metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma (NRSTS).

Patients were randomized to receive standard induction chemotherapy (IVADo/IVA) or standard chemotherapy plus bevacizumab (7.5mg/kg every 3 weeks), surgery and/or radiotherapy, followed by maintenance chemotherapy (low dose cyclophosphamide and vinorelbine) with bevacizumab added to the experimental arm at 5mg/kg every 2 weeks of each cycle. The primary objective was event free survival (EFS).

154 patients in the study. 80 with standard chemotherapy and 74 standard chemotherapy plus bevacizumab. Disease histologies were evenly matched in the two arms.
The addition of bevacizumab to the chemotherapy backbone used in metastatic soft tissue sarcoma appeared tolerable but the primary end-point of event free survival did not show statistically significant improvement.

The lack of statistical significance for the primary end point may reflect the fact that the sample size, although realistic for this rare tumor population, was inadequate to show a treatment effect.

❖ While the addition of bevacizumab to standard chemotherapy for metastatic soft tissue sarcoma in children and adolescents was well tolerated the primary end-point of event free survival did not show statistically significant improvement.

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45 Gy is not sufficient radiotherapy dose for Group III orbital embryonal rhabdomyosarcoma after less than complete response to 12weeks of ARST0331 chemotherapy

Ermoian, RP et al, 2017, Pediatric Blood and Cancer

In this paper, the COG retinoblastoma group assessed the efficacy of 45 Gy local radiotherapy in patients with Group III orbital embryonal rhabdomyosarcoma (ERMS) enrolled on the low-risk study ARST0331. More particularly, they assessed whether initial response to chemotherapy predicted outcome for patients with unresected orbital ERMS.

62 patients on ARST0331 had orbital Group III disease. Patients received four cycles of VAC followed by four cycles of VA over 22 weeks and RT starting after 12 weeks of chemotherapy. Complete response (CR) was defined as complete disappearance of the tumor by exam and imaging. Local recurrences, EFS and OS were also reported.

The 5-year EFS and OS for the entire cohort of 62 patients was 87% and 97% respectively. Fifty-three patients were evaluable for the response analysis. Fifteen patients had a CR to VAC chemotherapy. Local control on this study was worse than in the previous IRS-IV study with more intensive therapy.
Although none of the patients with early CR relapsed, this difference did not reach statistical significance.

This study was not the primary outcome of ARST0331 and was apparently underpowered to detect small differences. Also, this study did not explore the utilization of PET CT as a way to assess response after 12 weeks.

❖ For patients with Group III orbital ERMS with CR after induction chemotherapy, the ARST0331 treatment algorithm is associated with inferior local control than was achieved on the more intensive IRS-IV therapy and warrants consideration of different local treatment algorithms. Dose escalation to 50.4 Gy for patients with Group III
orbital ERMS on a backbone of ARST0331 chemotherapy could be an option to explore.

Paratesticular rhabdomyosarcoma in children and adolescents-Outcome and patterns of relapse when utilizing a nonsurgical strategy for lymph node staging: Report from SIOP Malignant Mesenchymal Tumour 89 and 95 studies.

Roger, T et al, 2017, Pediatric Blood and Cancer

Surgical staging with ipsilateral retroperitoneal lymph node sampling is currently required for all children aged 10 years and older with paratesticular rhabdomyosarcoma on COG-STS studies. However, node dissection was not routine in Europe for adolescents with resected paratesticular rhabdomyosarcoma. Many European investigators relied on radiographic, rather than surgical-pathologic assessment, for retroperitoneal lymph node involvement because of the high morbidity of the surgical assessment. This study aims to review all patients with non-metastatic paratesticular RMS enrolled in International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumour (MMT) 89 and 95 trials and to report the outcomes and patterns of relapse when utilizing a nonsurgical strategy for lymph node (LN) staging.

Patients with paratesticular rhabdomyosarcoma were evaluated with imaging but did not undergo routine ipsilateral lymph node sampling. Biopsy or fine-needle aspiration cytology was performed on regional nodes if there was clinical or radiologic uncertainty about LN involvement.

159 patients with localized paratesticular RMS were included in this study between 1989 and 2003. 25% of these patients were more than 10 years of age. Thirty-one percent of stage N0 patients of age ≥10 years developed node relapse, compared with 8% of N0 patients aged 5 years (42%) and three nodal relapses occurred in 15 patients with tumors >5 cm (20%, P = 0.27) (size was unknown for one patient).

When nodal relapse occurred in this group, it was predominantly in patients with tumors >5 cm. This was not statistically significant likely due to the size of the population. This study did not explore if there is a superiority of one of the 3 different radiological imaging (US, CT, MRI). Finally, the utilization of PET scan as part of the disease staging is also a possible way to improve staging without the morbidity of surgical assessment. It is something that can eventually be explored.

❖ Older patients with paratesticular rhabdomyosarcoma (≥10 years) have a significant risk of LN relapse. These results support a surgical approach to LN staging in this subgroup of patients. The SIOP MMT group subsequently recommended ipsilateral lymph node sampling for all patients aged 10 years and older.

A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study

Banerjee, A et al, 2017, Neuro-Oncology

Low grade gliomas (LGGs) are the most common type of brain tumor in children with excellent overall survival. Still, patients with incomplete resection and treatment/tumor progression can be affected with significant morbidity. MAP kinase pathway overexpression was commonly encountered (BRAF V600E mutation and BRAF:KIAA1549 fusion are the most commonly described). Selumetinib is an oral MEK inhibitor (downstream from BRAF in MAPK pathway), which has shown efficacy in xenografts and adults (for pediatrics, see recent NEJM article). This is the phase 1 study for selumetinib in LGG to describe the toxicity profile, phase 2 dose recommendation and pharmacokinetics.

Patients between 3-21 years of age with pathologically proven LGG were included who have been treated with 1 or more previous regimens. Patients with optic pathway gliomas and prior BRAF or MEK inhibitors treatment were excluded. Pharmacokinetics were measured after the first dose of selumetinib. Pathology specimens were tested for MAPK pathway activation using immunohistochemistry for ERK (downstream from BRAF). Where possible, FISH was done to look for BRAF fusion and PCR was done to look for BRAF mutation.

Thirty-eight patients were enrolled on the study. Most patients had pilocytic astrocytoma (n=22) and were previously treated with chemotherapy (n=20) or chemotherapy plus radiation (n=18). All patients with pathology evaluated (n=20) had evidence of MAPK activation with IHC positive for ERK. 25 mg/m2/dose were identified as the recommended dose for phase 2 with 3/24 patients experiencing DLTs (all were over 12 years of age, and rash, diarrhea and elevated CPK being the most common).
There were 5 PRs at the recommended dose level (3 with BRAF fusion or mutation, 1 with both - fusion and mutation - and 1 with tissue that could not be evaluated). Seventeen patients progressed (7 while on treatment, 10 after discontinuing selumetinib. Median follow up in patients who did NOT progress was 7.7 months.
PK values were consistent through different doses and age groups.

There is no standard for measuring response to LGG through different studies. Another limitation is that not all patients had tissue to characterize the method of activation of MAPK pathway. The authors only screened for the most common alterations. This may be important given that previous studies have demonstrated paradoxical activation of the MAPK pathway with progression seen in patients with BRAF fusion who are given a BRAF inhibitor (i.e. dabrafenib), however this did not seem to be the case in this trial.

❖ Selumetinib is tolerable in children, and the RP2D is 25 mg/m2/dose. Some activity was seen although further studies are needed with stratification based on type of alteration and NF-1 status.

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

Risk Factors for Subsequent Central Nervous System Tumors in Pediatric Allogeneic Hematopoietic Cell Transplant: A Study from the Center for International Blood and Marrow Transplant Research (CIBMTR)

Gabriel, M et al, 2017, Biology of Blood and Marrow Transplantation

This is a case control study examining the cumulative incidence of CNS neoplasms in patients after allogeneic stem cell transplant. This review was conducted by CIBMTR which comprises the largest database of HSCT information.

Using the CIBMTR database the review was conducted from 1976 to 2008 and included survivors at least one year out of transplant. All CNS tumour cases were reviewed and further information was obtained from the treating centre. A case-control comparison was performed where controls were HSCT patients who did not have a diagnosed CNS tumour. Cox regression models were used to analyze the data from the entire cohort and identify risk factors.

59/8720 participants developed CNS tumours, with half being either astrocytoma or glioblastomas. Compared to the general population, those undergoing allogeneic stem cell transplant for a hematologic malignancy had a 33 times higher than expected rate of CNS tumours (95% CI, 22.98 to 45.77; P=0.0001). The cumulative incidence of subsequent CNS tumours was 1.29% (95% CI .87 to 1.87) at 20 years after transplant. The risk factors for developing CNS tumours were: having an unrelated donor transplant, CNS disease before transplant and radiotherapy exposure before conditioning were risk factors for developing a CNS tumour.

This study is limited by its retrospective nature, and depends on the accuracy of submitted data. This is the first report of this kind and so replication would strengthen the findings.

❖ In the large CIBMTR database no CNS tumours were found in patients transplanted for non-hematologic malignancies or who received non-myeloablative or reduced intensity conditioning (total of 4730 patients). Patients transplanted for hematologic malignancies are at an increased risk of developing a CNS tumour compared to the general population. The identified risk factors from this study are pre-transplant radiation exposure and an unrelated donor.

Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Inherited Bone Marrow Failure Syndromes: Consensus Statement From the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects After Pediatric HCT

Dietz, AC et al, 2017, Biology of Blood and Marrow Transplantation

❖ This is a consensus paper regarding long-term follow-up screening that should occur for patients transplanted for inherited bone marrow failure syndromes. The paper specifically discusses follow-up for Fanconi's Anemia, Dyskeratosis Congenita and Diamond-Blackfan Anemia.

Recent Developments in Radiotherapy

Citrin DE, 2017, New England Journal of Medicine

❖ This is an interesting review of the advancements in radiotherapy including treatment planning, combination therapy, and the use of radiosensitizers. Minimal discussion of hot topics in paediatrics such as proton therapy and immune modulation.

Stories that heal: Understanding the effects of creating digital stories with pediatric and adolescent/young adult oncology patients

Laing, C et al, 2017, Journal of Pediatric Oncology Nursing

This qualitative study aimed to explore if and how the creation of digital stories can be used as a therapeutic tool for children/young adults with cancer and their family members. Digital storytelling comprises multiple modalities (ex. music, narration, photos) to tell a story.

Participants were children/young adults from 5-39 years old who had either undergone treatment or were currently in treatment for a pediatric malignancy. They also included family members of cancer patients/survivors. Participants were assisted in making a digital story on iMovie through about 3, 2-hour sessions. They then underwent an interview to discuss the experience of making the story. Data analysis was with a hermeneutic approach, which aimed to deepen understanding of the effect of making a digital story on the participants.

Participants found that making the story was effective in helping others to understand their experiences. Those who were further out from treatment found that it helped them to heal or move on, whereas children on treatment enjoyed the distraction the experience provided. Many participants were surprised to find the therapeutic value in making a digital story. They reported that making the story helped in understanding and making sense of what they had experienced.

This was a small study with only 16 participants, who had a wide range of diagnoses, ages and distance from treatment. The researchers identified the different therapeutic effect of digital storytelling on those who were in treatment and those further from it. However, there was limited interpretation on differences in age, diagnosis and prognosis.

❖ This study suggests that digital storytelling may be a helpful adjunct therapeutic intervention for children and adolescents who are experiencing cancer, whether it is themselves or as a sibling.
