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BestBits of the Pediatric Hematology Oncology literature

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.

In this issue, we see how two technologies that have revolutionized the world of research genetics are starting to have a major impact in the treatment of hematologic diseases. Next generation sequencing has driven down the cost and increased the speed of generating genome-wide data over the past decade. Although the first application of this technology that we tend to think of is whole genome sequencing, Wood et al show how very deep sequencing of a small selection of genes can be used to monitor leukemia clones and therefore increase the sensitivity of minimal residual disease detection.

The other revolutionary technology has been the use of the CRISPR-Cas9 system for targeted gene editing. It has been only five years since this technique was developed but it has now nearly reached the clinical trial stage. Antoniani et al show that deletion of the beta-globin locus by Cas9 in human hematopoietic stem cells leads to increased production of HbF. This change in genotype would be expected to markedly decrease the transfusion requirement for patients with beta-thalassemia through an autologous transplant thereby avoiding all the complication of allogeneic stem cell therapy. These results form the basis of a clinical trial now working its way through the regulatory system.

Of course, older gene therapy technologies are still being investigated and Miesbach et al describe how modifications to adenovirus vectors can improve outcomes for patients with factor IX deficiency treated with gene therapy.

The world of genomics is being rapidly changed by next generation sequencing and gene editing. The speed with which these technologies have come to the clinic is astounding and drives home how quickly the world of hematology and oncology is changing. BestBits continues to be here to help you keep up with the rapidly evolving literature so read on and enjoy!

Editors

Reviewers


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BestBits of the Pediatric Hematology Oncology Literature

Section 1. General Hematology, Thrombosis & Transfusion Medicine

Induction of fetal hemoglobin synthesis by CRISPR/Cas9-mediated editing of the human β-globin locus

Antoniani, C et al, 2018, Blood

Synthesis of fetal gamma-globin is usually silenced to a large degree after the first months of life. Upregulation of gamma-globin production was shown to mitigate the severity of beta-globin diseases like beta-thalassemia and sickle cell disease. This report investigated whether upregulation of fetal hemoglobin through genome editing might be beneficial in beta-globin diseases.

Large deletions in the beta-globin gene lead to hereditary persistence of fetal hemoglobin. Mutations in these locations were introduced with a CRISPR/Cas9 system in apheresed blood progenitor cells of patients with sickle cell disease or beta-thalassemia.

Of different deletions tested, a 13.6kb measuring deletion (largest) was the most effective with robust fetal hemoglobin production. The same was true for an inversion that spanned the same region. Half the edited cells and about 1/3 overall carried the biallelic rearrangement.

So far, this is a cell line experiment and results cannot directly be transferred to humans. It remains to be proven that these genetically modified cells do engraft in a recipient with sickle cell disease or thalassemia.

❖ This is a promising novel approach on how to treat beta-globin diseases with gene editing of patient-derived cells to increase hemoglobin F production. A clinical trial utilizing this approach is in the works and has already passed several regulatory hurdles.

Immune tolerance induction: What have we learned over time?

Brackmann, HH et al, 2018, Haemophilia.

❖ Good review on immune tolerance induction including different protocols to tackle inhibitors in hemophilia.

Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B

Miesbach, W et al, 2018, Blood

Gene therapy for hemophilia B is an area of active investigation. The first trial using an adeno-associated virus (AAV) - 8 vector demonstrated durable Factor IX (F9) expression, with reduction in bleeding rates and usage of factor replacement products. However, T-cell activation in response to the viral vector led to loss of transgene, which was temporally associated with transaminitis. The AAV-5 vector has a preferential immune profile, with lower prevalence of neutralizing antibodies and an apparent lack of cellular immune response. As such, it may be a better vector for F9 gene therapy.

10 adults with Hemophilia B either on prophylactic therapy or bleeding manifestations were given a single IV infusion of AMT-060 - a codon-optimized wild-type F9 within an AAV-5 vector. Safety outcome measures included neutralizing antibodies, F9 antibodies, and treatment-related adverse events. Efficacy outcomes included use of F9 concentrates, F9 plasma levels, bleed data, and joint health scores.

6 participants experienced a total of 14 adverse events, most of which were mild, and three had mild elevations of liver transaminases. No patients developed any neutralizing antibodies to AAV-5 or F9. F9 activity rose in all participants and

remained stable - patients in the lower-dose cohort achieved mean levels of > 2 U/dL and those in the higher-dose cohort achieved levels of >5 U/dL. Eight of the 9 patients on prophylaxis were able to stop, with a total reduction in F9 use of 79% across all participants. This is a small cohort with a limited duration of follow up. Long term durability of the transgene remains to be determined.

❖ Utilization of the AAV-5 vector for F9 gene transfer was not associated with vector specific T-cell responses or loss of F9 activity, suggesting it may be a preferable gene delivery system.

Targeting anticoagulant protein S to improve hemostasis in hemophilia

Prince, R et al, 2018, Blood

Current therapy for hemophilia involves replacement of the missing coagulation factor, which has numerous drawbacks including frequent IV infusions and risk of inhibitor formation. Newer approaches have explored gene therapy, antibody-based mimetic therapy, and targeting of coagulation inhibitors to restore thrombin generation. Protein S is a co-factor to activated protein C and tissue factor pathway inhibitor (TFPI) and is therefore a key regulator of thrombin generation.

A protein S (ProS) knockout mouse model was used to evaluate the potential role of protein S inhibition in management of hemophilia. This model was interbred with Factor 8 (F8) and Factor 9 (F9) knockout mice to generate mice which were co-deficient in either F8 or F9 and ProS. These mice were then studied in several bleeding models, including tail clipping and acute hemarthrosis, as well as a model of tissue factor-induced pulmonary embolism.

The model demonstrated that the loss of thrombin generation from F8 or F9 deficiency rescued the ProS deficient mice from thromboembolic complications, although it did not prevent induced pulmonary embolism. Tail bleeding was limited but not completely abrogated in F8 and ProS deficient mice, although ProS deficient mice with F8 or F9 deficiency were protected from acute hemarthrosis. Subsequent studies demonstrated that both ProS and TFPI are expressed in the synovium of both mice and human patients, which may explain this effect. As a final human proof of concept, the research group demonstrated that ProS inhibition in plasma restored thrombin generation in patients with F8 deficiency. As an animal study, this requires further evaluation in human clinical trials.

❖ Targeting ProS can improve hemophilia in a mouse model, both as an improved bleeding phenotype and protection against hemarthrosis. This may lead to the development of novel therapies for patients with hemophilia.

Gene Therapy in Patients with Transfusion-Dependent Beta-Thalassemia

Thompson, AA et al, 2018, The New England Journal of Medicine

This study evaluates the safety and efficacy of a lentiviral beta-globin gene therapy compared to long-term red-cell transfusions in patients with beta-thalassemia. This study reports interim results from two companion phase I and II clinical studies, specifically evaluating the LentiGlobin BB305 vector using a multi-center, non-randomized, open-label single-dose approach.

Patients between the ages of 5 and 35 years with any genotype of transfusion-dependent B-thalassemia were eligible. Patients had hematopoietic stem cells harvested by apheresis. CD34+ cells were transduced with BB305. Conditioning occurred with myeloablative IV busulfan followed by infusion of the LentiGlobin vector-manipulated stem cells.

22 patients were treated on the study. Treatment with the BB305 vector-manipulated stem cells reduced or eliminated the need for transfusion therapy in all 22 patients. In patients 12/13 patients with a non-β0/β0 genotype and 3/9 with a β0/β0 genotype became transfusion-independent. In those who continued to require transfusions, transfusion volume was decreased by 73%. There were no major adverse events, apart from those typically associated with autologous stem cell transplantation.

Small study in 22 patients. The treatment requires autologous stem cell transplantation and a specific lentiviral product that is not yet widely available. Safety has not yet been fully evaluated as long-term or rare side effects cannot be determined from only 22 patients.

❖ This study presents an exciting alternative to allogenic hematopoietic stem cell transplantation in patients with transfusion-dependent beta-thalassemia. Further research is required to better characterize the safety profile.

Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency

Shapiro, AD et al, 2018, Blood

Congenital plasminogen deficiency is an exceedingly rare autosomal recessive disorder characterized by pseudomembranous lesions on mucous membranes throughout the body, abnormal wound healing and infertility. With the highest severity in infants and children, it is caused by mutations in PLG and is estimated to affect 1.6 individuals per million. Treatment is usually surgical excision of the lesions, although plasminogen concentrates purified from human plasma are being developed as an IV replacement therapy.

This is an open label study of human plasminogen given every 2-4 days based on pharmacokinetic (PK) studies, to achieve a trough plasminogen level of 10% above the patient's baseline. The primary outcome was the ability to obtain this PK endpoint; secondary outcomes were overall clinical success in both the number and size of lesions or change in organ function. Clinical examination of visible lesions and medical imaging of non-visible lesions were used to quantify change.

14 patients, including 5 children, were enrolled. All achieved the primary endpoint, with three patients having transient falls in their trough levels associated with interruption of the infusion schedule. PK studies reveal an approximate 2-week interval to achieve steady state levels. Clinical endpoints also had a 100% success rate, with resolution or improvement of all visible and non-visible manifestations assessed at baseline. The therapy was well tolerated in all patients. Because of the very small sample size, there were no power calculations or statistical determinations, which the authors acknowledged a priori.

❖ Replacement therapy with human derived plasminogen effectively increased plasminogen activity and improved clinical symptoms. This is an important advance given the limitations of other current treatment options.

Immunogenicity, efficacy and safety of Nuwiq® (human-cl rhFVIII) in previously untreated patients with severe haemophilia A-Interim results from the NuProtect Study.

Liesner, RJ et al, 2018, Haemophilia

Nuwiq® (Human-cl rhFVIII) is a fourth generation recombinant FVIII. This is an ongoing, prospective, multicenter, multinational, open-label, non-controlled, phase III study (NuProtect study) of 110 male previously untreated patients, which aimed to assess immunogenicity, efficacy and safety of Nuwiq in severe Hemophilia A patients. Here, they report data from a subgroup of 66 patients treated with Nuwiq for up to 100 exposure days (EDs) or 5 years.

Patients received Nuwiq for standard prophylaxis or on-demand treatment, and for treatment of breakthrough bleeds or surgical prophylaxis, as required. The recommended dose for standard prophylaxis was 20-50 U FVIII/kg. The dosage and duration for treating breakthrough bleeds, on-demand treatment and during surgical prophylaxis depended on the location and extent of bleeding, and the clinical condition of the patient. The primary objective is to assess the immunogenicity of Nuwiq (inhibitor activity ≥0.6 BU) using the Nijmegen-modified Bethesda assay at a central laboratory.

High-titre (HT) inhibitors developed in 8 of 66 patients after a median of 11.5 EDs (range 6-24) and low-titre inhibitors in 5 patients. Cumulative incidence was 12.8% for HT inhibitors and 20.8% for all inhibitors. Efficacy was rated as “excellent” or “good” in treating 91.8% of bleeds and for 8 (89%) procedures. Nuwiq was generally well tolerated. The majority of AEs were mild.

Interim analysis included only the 66 patients who were treated for ≥20 EDs with Nuwiq. As almost all patients enrolled across 14 countries in this interim analysis were Caucasian, no data were collected for patients of African descent who are assumed to be at higher risk of inhibitor development.

❖ These interim data showed that Nuwiq was well tolerated and had good efficacy in Hemophilia A. Cumulative incidence of inhibitors was 12.8% for High titre and 20.8% for all inhibitors.

Section 2. Leukemia, Lymphoma & Bone Marrow Transplantation

Integrated molecular profiling of juvenile myelomonocytic leukemia

Murakami, N et al, 2018, Blood

JMML is a rare myeloid neoplasm with few therapeutic options. The majority of cases are driven by mutations in the RAS pathway and several molecular and clinical prognostic markers are known. This research group used multi-omic profiling to find driver events in the ~20% of patients without RAS mutations and to identify new prognostic markers.

150 children were included in this study although not all patients were evaluated by each modality. The majority of data was generated through high-throughput exome sequencing, high-throughput mRNA sequencing, and a DNA methylation array (the now-defunct Illumina 450K array).

1) Three children without RAS pathway mutations were found to have ALK (n = 2) or ROS1 (n = 1) fusions. Crizotinib (a TKI effective against ALK and ROS1 activity) decreased proliferation in cell lines obtained from these patients. One patient with an ALK fusion and refractory disease had a clinical response to Crizotinib bridging her to transplant.
2) The group identified 2 DNA methylation profiles and 4 RNA expression profiles. LIN28B (a developmental gene involved in microRNA activity and affected in multiple cancers) was both differentially methylated and expressed. The "hypermethylation" profile and "AML-like" profile both carried poor prognosis.

When creating tumor profiles using genome-wide data such as DNA methylation or RNA sequencing, investigators must make many choices (e.g. how to normalize and filter the data, which coordinates to use, how to define a subgroup etc). In this study, the selected sequencing methodology is debatable, so analyses can only be considered robust if they are convincingly replicated - otherwise they may be artifacts of upstream analytical decisions.

❖ This is a thorough analysis of a large number of JMML cases. The finding of ALK/ROS1 fusions - even though rare - should prompt us to look for these fusions in our refractory patients keeping in mind the possible use of targeted agents. The DNA methylation and expression profiles require replication before integration with clinical decision making.

Early Nutrition Intervention Attenuates Weight Gain for Pediatric Acute Lymphoblastic Leukemia Patients in Maintenance Therapy

Hill, R et al, 2018, Journal of Pediatric Hematology/Oncology

Children with ALL are at increased risk for long-term obesity. Recent studies have indicated that weight gain begins during ALL therapy, particularly during induction and maintenance phases, and often persists beyond treatment. There are no published strategies specific to the pediatric ALL population to reduce obesity.

In a retrospective manner, this study investigated the impact of a 3-visit nutrition intervention early in maintenance therapy involving 3 one-on-one visits with a registered dietician. The visits focused on the child's current nutritional status and goals and provided handouts. 33 patients who received the intervention were compared with a control group of 34 historical patients. BMI was recorded at diagnosis, end of induction, beginning of delayed intensification, day 1 of maintenance therapy and monthly for 12 months.

As expected, the mean BMI z-score increased from diagnosis to day 29 of induction, dropped in delayed intensification and then rose throughout maintenance therapy. There was no statistically significant difference between the BMI z-score of the control group and the intervention group at the different time points. On multivariate analysis, the intervention group's BMI z-scores increased less over maintenance therapy compared to the control group (P=0.0001). However, the intervention was less effective for patients who gained more in BMI z-scores between diagnosis and the start of maintenance therapy.

Information on behaviors including diet and exercise and other indicators of body composition including fat composition were not collected as it was a retrospective chart study. The patients who received the intervention was at the discretion of their health care team. The small sample size, potential selection bias, and use of a historical control severely limits the generalizability of the results.

❖ This study does not provide evidence for efficacy of this particular intervention but does not mean that educational interventions are not useful. Future prospective trials should be well designed and draw from the extensive experience in the adult literature.

Measurable residual disease detection by high-throughput sequencing improved risk-stratification for pediatric B-ALL.

Wood, B et al, 2018, Blood

The initial response to therapy is a key prognostic factor in pediatric B-ALL. This is currently determined as the level of measurable residual disease (MRD) at the end of Induction chemotherapy. Normally determined by flow cytometry (FC), this leads to limitations in the analytic sensitivity and difficulty in clinical standardization of the technique. As well, changes in antigen expression on the lymphoblasts during therapy may obscure detection by FC. High-throughput sequencing (HTS) of the immunoglobulin and T-cell receptor loci may represent a superior methodology for detection of MRD.

Paired pre-treatment and end of induction samples for patients enrolled in front-line childhood B-ALL treatment trials were identified for MRD evaluation. Both FC and HTS were performed on the samples. For HTS, pre-treatment samples were assessed for clonality by deep sequencing of the immunoglobulin (IGH@) gene. A dominant sequence determined for identification at end of induction, as an indicator of MRD. The amount of DNA was extrapolated to the equivalent total nucleated cell count, to give a comparable metric to MRD by FC.

607 evaluable samples were studied, and HTC and FC showed good correlation for both event-free and overall survival at an MRD of 0.01%. Samples where MRD was above the threshold by HTS but not FC were found to have an intermediate prognosis, suggesting that it had a higher analytic sensitivity for low levels of MRD. Patients with no trackable rearrangement of the immunoglobulin heavy chain by HTS, suggesting an earlier stage neoplastic transformation, had a poorer prognosis.

HTS required initial access to heavy leukemic involvement to identify an appropriate target sequence, and cannot be used in patients lacking a detectable immunoglobulin or T-cell receptor rearrangement. Turn-around time is also longer than with FC and the technology is currently more expensive.

❖ HTS offers an improved analytic platform for measurement of MRD in pediatric B-ALL, with the same threshold as standard FC.

Acute Kidney Injury in Pediatric Patients Receiving Allogeneic Hematopoietic Cell Transplantation: Incidence, Risk Factors, and Outcomes

Koh, KN et al, 2018, Biology of Blood and Marrow Transplantation

Acute kidney injury (AKI) is a common adverse event after hematopoietic cell transplantation (HCT). Although several small studies have evaluated AKI after pediatric HCT, large-scale studies are lacking. In addition, most earlier studies did not use standardized criteria of AKI.
This is a retrospective study, applied on a large pediatric population to establish the incidence and outcomes of AKI and to determine the risk factors associated with AKI after allogeneic HCT.

The study retrospectively analyzed data from 1057 pediatric and adolescent patients who received HCT from January 1991 to December 2015. Modified AKI network (AKIN) classification was used.

The 100-day cumulative incidences of all stages of AKI, stage 3 AKI, and AKI requiring renal replacement therapy (RRT) were 68.2%, 25.0%, and 7.6%, respectively. Overall survival at 1 year was not different between patients without AKI and those with stage 1 or 2 AKI but was significantly different between patients without AKI and patients with stage 3 AKI with or without RRT requirement (66.1% versus 47.3% versus 7.5%, respectively; P.001). Age, year of transplantation, donor type, SOS, and acute GVHD were independent risk factors for stages 1 through 3 AKI. Age, donor, conditioning regimen, number of HCTs, SOS, and acute GVHD were independent risk factors for AKI requiring RRT.

This study does provide a large-scale and comprehensive analysis of AKI from HCT yet with some limiting factors.
First, relying on serum creatinine as a sole measure of AKI with no data on urine output or state of hydration carries potential flaws in the applicability of the modified AKIN criteria. As in these categories of patients receiving HCT for prolonged, complex illnesses, serum creatinine may remain low despite a marked reduction in glomerular filtration rate. Serum creatinine is influenced by multiple factors including diet and muscle mass.
Second, patient enrolment age up to 27 years including young adults might hamper conclusions for pediatric patients.
Third, including patients who received multiple transplants, yet their study enrolment renal condition was not elucidated.

❖ AKI was a prevalent adverse event affecting more than two-thirds of pediatric recipients receiving allogeneic HCTs. Notably, 25% of patients experienced severe stage 3 AKI according to the AKIN criteria, which greatly affected survival outcomes.

Low incidence of osteonecrosis in childhood acute lymphoblastic leukemia treated with ALL-97 and ALL-02 study of Japan Association of Childhood Leukemia Study Group

Sakamoto, K et al, 2018, Journal of Clinical Oncology

Osteonecrosis (ON) is a serious complication of ALL treatment and can affect quality of life on the long term. Incidence is variable and identified risk factors include older age, female sex, dose and type of corticosteroids, combination of dexamethasone and L-asparaginase, and ethnicity. This retrospective analysis of cohorts of Japanese patients with ALL examines the incidence, risk factors, and treatment of ON.

Incidence and characteristics of ON were determined in patients with ALL (Pre-B ALL or T-cell ALL) enrolled in 2 studies from the Japanese Association of Childhood Leukemia Study (JACLS) group (n=635 ages 1-15 years for ALL-97 and n=1,027 ages 1-18 years for ALL-02). In both studies, L-asp was administered with prednisolone and dexamethasone was not used.

24/1,662 patients had symptomatic ON during/after treatment. 15/24 were female. Most frequent site was the femoral head (17/24). 5-year cumulative incidence of ON in patients age 10 or older was 7.2% (ALL-97) and 5.9% (ALL-02), compared to most previous studies that report much higher incidence of ON, usually exceeding 10%. 11 patients required orthopedic surgery. In evaluating the risk factors, for both protocols the only significant risk factor was age greater than or equal to 10 years.

ALL-97 collected data prospectively while ALL-02 collected data retrospectively via questionnaire. Patients post BMT were excluded. Japan has a comparatively homogeneous population and thus their underlying genomic risk may be different from their genetically heterogeneous European or North American counterparts. Genomic data (such as SNP array data) might be helpful in untangling risk factors for ON.

❖ Low frequency of ON in the JACLS studies compared to previous studies. Although the cumulative steroid dose and amount of dexamethasone was equivalent to previous COG/CCG/AIEOP trials, it was not co-administered with asparaginase so this may be an important risk factor. Genomic risk of ON was not assessed however, and this may also be an important difference.

Section 3. Oncology: Solid Tumors and Neuro-Oncology

Paediatric dysgerminoma: Results of three consecutive French germ cell tumours clinical studies (TGM-85/90/95) with late effects study

Duhil de Be´naze, G et al, 2018, European Journal of Cancer

Dysgerminoma is an ovarian germ cell tumour and a rare type of childhood cancer. Treatment for dysgerminoma consists of surgery followed by adjuvant radiation therapy in early years and adjuvant chemotherapy in more recent years.

In this prospective cohort study located in France, patients ≤ 18 years with ovarian dysgerminoma were treated according to three consecutive treatment protocols: TGM-85, 90 and 95. Treatment consisted of primary unilateral or bilateral oophorectomy followed by a) prophylactic radiation therapy 1985 – 1998) or b) wait-and-see strategy for localized disease or platinum-based chemotherapy for advanced disease (1998 - 2005). Patients were assessed for late effects either by a clinical follow-up visit or by a questionnaire with emphasis on fertility, renal function, and hearing impairment.

This study includes 48 patients who had a median age of 12.8 years (range 7 – 18.7) at diagnosis and a median follow-up time of 14.7 years (range 1.4 – 28.4). Twelve patients had a bilateral oophorectomy.

Follow-up data were available for 27/48 patients (14 clinical visits and 13 questionnaires). 13/17 patients who attempted pregnancy were successful - 5 requiring assisted reproduction technologies. 3/17 had Brock grade I ototoxicity and two patients Brock grade IV ototoxicity. 24/25 patients assessed had normal Renal function. Five-year EFS was 91.4% (three recurrences, one second neoplasm). One patient developed melanoma 16 years after therapy. Overall survival was 100%.

In this study, dysgerminoma treatment was heterogeneous due to three different treatment protocols and therefore associations between treatment exposure and late effects are difficult to draw. Besides, only half of the patient populations was evaluated for late effects, therefore the prevalence of late effects might be biased. The very small numbers limit generalizability but it may be difficult to recruit larger numbers in this rare disease.

❖ Ovarian dysgerminoma is a rare childhood cancer with an excellent prognosis even in advanced disease. Treatment for dysgerminoma significantly affects fertility, but ototoxicity and renal impairment are rare late effects. The numbers are small in this study and other information on platinum toxicity must be taken into account clinically.

Radiation Therapy to Sites of Metastatic Disease as Part of Consolidation in High-Risk Neuroblastoma: Can Long-term Control Be Achieved?

Casey, DL et al, 2018, International Journal of Radiation Oncology Biology Physics

Radiation therapy (RT) to metastatic sites as part of consolidative therapy in neuroblastoma is standard in Children's Oncology Group protocols, but has not been rigorously studied. Retrospective review of 159 HR NB patients treated with RT that was directed to 244 metastatic sites at Memorial Sloan Kettering Cancer Center between years 2000-2015. 21 Gy BID (twice-a-day) was typically given.

The 5-year local control (LC) rate (of the irradiated metastatic site) was 81%. Sites that became negative on MIBG after induction chemotherapy had a higher LC rate as compared to those that were persistent after induction treatment (92% vs. 67%, respectively; statistically significant). Persistent disease after induction chemotherapy was the only significant prognostic factor for LC on multivariable analysis. Importantly, LC at irradiated metastatic sites was associated with an overall survival benefit.

A majority (62%) of patients had one irradiated metastatic site. This study does not answer the question about whether aggressive irradiation of all metastatic sites in patients with numerous sites of metastatic neuroblastoma is helpful. The authors commented: "The maximum number of sites that can and should be irradiated as a part of consolidative therapy remains unknown." This study could not tell us if persistent metastatic sites after chemotherapy should receive RT dose-escalation beyond 21 Gy. The radiation was delivered twice-a-day as part of the MSKCC standard; this is not typically done at other cancer centers due to the challenging logistics of BID radiation treatment.

❖ This retrospective study demonstrates that local control of metastatic sites in patients with neuroblastoma is important and associated with a survival benefit. Patients with metastatic sites that resolve after initial chemotherapy should be considered for RT to ensure local control.

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

Risk of hepatitis B virus reactivation in patients treated with ibrutinib

Hammond, SP et al, 2018, Blood

Hepatitis B reactivation has been reported in patients with cancer receiving targeted therapies including mammalian target of rapamycin (mTOR) inhibitors, monoclonal antibodies and tyrosine kinase inhibitors. Ibrutinib is a Bruton tyrosine kinase inhibitor which affects B cell signaling, used in adult lymphomas (CLL, mantle cell lymphoma) and Pediatric Non-Hodgkin lymphoma.

This is a letter to the Editor which reports a 57-year-old man with CLL who had a Hepatitis B reactivation nearly 4 years after starting on ibrutinib for progression of disease. The authors then looked at the group of patients who received Ibrutinib at Dana-Farber Cancer Institute between 2010 and 2016 to see what the incidence of Hepatitis B reactivation was for Ibrutinib.

2/71 patients developed Hepatitis B reactivation. One was the index patient described above and the other was a 75-year old man with CLL. The latter received antiviral therapy for Hepatitis B. Overall incidence was 9.5%. The clinical significance of the infection or low-level viremia during ibrutinib treatment is unclear from this study of only two cases. There was a review of the literature with tyrosine kinase inhibitors and Hepatitis B reactivation in Hematology last year. (Chang et al (2017) Hematology)

❖ Hepatitis reactivation is an important consideration when using targeted therapies, even if infection was resolved prior to starting cancer therapy.

Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update Summary

Oktay, K et al, 2018, Journal of Oncology Practice

ASCO first published evidence-based clinical practice guidelines on fertility preservation in 2006 with an update in 2013. This is the most recent iteration of the guideline which although it is adult focused, also applies to the pediatric population.

The guideline re-affirms some of the previous recommendations including a discussion of the possibility of infertility as early as possible before treatment starts, which is thought to reduced distress and improve quality of life. The discussion should be re-addressed after completion of therapy. Options for post-pubertal males continue to include sperm cryopreservation, ideally done pre-treatment to ensure optimal quality. With technologies like IVF and intra-cytoplasmic sperm injection however, cryopreservation can still occur for patients on treatment if there is an urgency to begin therapy. Hormonal gonado-protection has not been shown to be effective. Testicular tissue cryopreservation and grafting of human testicular tissue remain experimental.

Options for women include embryo and oocyte cryopreservation. Oocyte preservation would be more feasible for a larger group of patients as it is no longer considered experimental. Flexible ovarian stimulation protocols can be initiated with less delay than previous and newer protocols including aromatase inhibitors would make stimulation feasible even for women with estrogen sensitive malignancies without an increase in their risk of cancer recurrence. Ovarian transposition during pelvic irradiation remains a viable option, although is not always successful due to scatter. There is conflicting evidence for GnRH agonists/ovarian suppression for fertility preservation. This can be considered when other methods are not feasible in young women. Perhaps most exciting is that while ovarian tissue cryopreservation remains experimental in North America, emerging data is very promising and some countries consider it nonexperimental. It is one of the best options for pediatrics and pre-pubertal patients. The safety of it in patients with leukemia is unknown. Adult guidelines; limited options remain for pre-pubertal children.

❖ A multitude of fertility preservation options exist for post-pubertal patients and should be discussed in a timely manner and on an ongoing basis. Exciting new data on the success of ovarian tissue transplantation may make this a viable option for a larger proportion of patients.

Palliative Care Consultation Should Be Routine for All Children Who Enroll in a Phase I Trial

Lord S, et al, 2018, Journal of Clinical Oncology

❖ This is an excellent article written by physicians of the palliative care team at the Hospital for Sick Children describing why all pediatric oncology patients enrolled in a phase I trial should receive a palliative care consultation.

Predictors of specialized pediatric palliative care involvement and impact on patterns of end-of-life care in children with cancer

Widger, K et al, 2018, Journal of Clinical Oncology

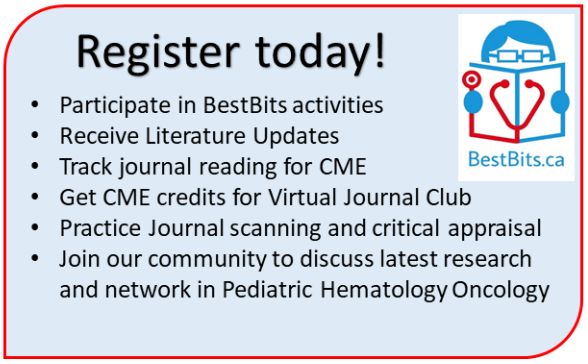
The quality of end of life care can be adversely affected by ICU admission and other intensive medical treatments. The objective of this retrospective cohort study was to link population-based clinical and health services databases to determine 1) which children with cancer access specialized pediatric palliative care (SPPC) and 2) the impact of accessing SPPC on the risk of experiencing high-intensity end-of-life care such as ICU admission during the last 30 days of life.

This study uses a combination of a provincial (Ontario) childhood cancer registry and health administrative data predicting the type of care received by a combination of billing codes, diagnostic codes, and SPPC databases. Children from 2000-2012 were categorized as having received either SPPC, generalized palliative care, or nor palliative care within 30 days of death.

572 children in total received care at one of the three institutions with SPPC teams and died during the period in which SPPC databases were available. 243 (42.5%) received care from SPPC team and 166 (29%) received SPPC for at least 30 days before death. 100 (17.5%) received general palliative care, which was based on not being in SPPC database but having physician billings for palliative care. 306 patients (53.5%) had no palliative care. SPPC involvement was significantly less likely for hematologic cancers, living in low-income areas, and living farther from treatment center. Accessing SPPC more than 30 days before death was associated with five-fold decreased odds of ICU admission and other high-intensity end-of-life care, including in-hospital death, whereas general palliative care had no impact.

Children who had SPPC or general palliative care for 30 days before death were counted as having no palliative care. Data did not include family preferences or goals of care. Difficult to generalize because health care systems and cultural attitudes about end-of-life care are variable.

❖ SPPC but not general palliative care is associated with lower intensity care at end-of-life. Access to SPPC is uneven. Strong evidence to support the creation and timely involvement of SPPC teams.



Registration is currently open to physicians and other healthcare professionals with an interest in Pediatric Hematology/ Oncology. You can tailor your registration preferences to receive bimonthly updates, be a journal reviewer and/or virtual journal club participant. You can update your preferences at any time.

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