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BestBits of the Pediatric Hematology Oncology literature

Introduction

Best Bits 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

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Oldenburg, J et al, 2017, New England Journal of Medicine

Hemophilia A patients with inhibitors face high morbidity including multiple bleeds and arthropathies. Emicizumab is a bispecific antibody that brings factors IX and X into close proximity thereby providing a tenase complex for the production of thrombin without the need for FVIII. This industry-sponsored phase III randomized open-label trial addressed the efficacy of this antibody in patients with hemophilia A and high inhibitor levels (BU > 5). Patients who previously received only episodic bypassing agents were randomized to receive either emicizumab or no prophylaxis. Patients >12 years who received prophylaxis with bypassing agents were non-randomly assigned to receive emicizumab. The primary endpoint was the rate of bleeding events.

In a comparison of the randomized arm, bleeding events were markedly decreased with emicizumab and ~60% of patients receiving the antibody had no bleeding over 24 weeks (only 1 patient was bleed-free in the control group). Adverse events were thrombotic (CSVT, TMA, superficial thrombophlebitis) and seemed to be highly correlated with concurrent receipt of emicizumab and activated PCC. Numbers were small but the effect was large enough that the size of the trial didn't need to be larger. The trial was also open label which may introduce a small amount of bias. The antibody hasn't been priced yet however and this may be a major clinical limitation in its use.

❖ Emicizumab is a highly efficacious prophylactic agent for patients with hemophilia A and high inhibitor levels. In the same issue there is an accompanying editorial by David Lillicrap, the world famous hemostasis specialist from Kingston, Canada.

Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy

Pasi, KJ et al, 2017, New England Journal of Medicine

Fitusiran is an RNA interference molecule that targets antithrombin RNA (and thereby decreases the amount of circulating antithrombin). This approach is theorized to decrease the number of bleeds in patients with hemophilia of any type and to potentially lower the requirement for prophylactic factor. This phase I study addressed the safety, pharmacodynamics, and pharmacokinetics of fitusiran. 4 healthy controls and 30 adults with hemophilia were enrolled. The primary outcome was plasma antithrombin levels.

Antithrombin levels decreased and thrombin levels concurrently increased both with weekly and monthly dosing. In an exploratory analysis, there were fewer bleeds/month after treatment than before. The safety profile was tolerable. This is a phase I study and so clinical utility is still limited.

❖ A new avenue for treatment of hemophilia and one of the few examples of clinical use of RNA interference therapy. The safety profile is encouraging - it will likely have phase III results reported shortly.

Family cord blood banking for sickle cell disease: a twenty-year experience in two dedicated public cord blood banks

Rafii, H et al, 2017, Haematologica

Hematopoietic stem cell transplantation (HSCT) is currently the only curative therapy for sickle cell disease. However, there remain challenges in both identifying appropriate donors, and reluctance to proceed to HSCT due to transplant-related toxicity. Umbilical cord blood transplant (CBT) from family donors has cure rates exceeding 90%, with low rates of GvHD. This retrospective review aimed to assess the characteristics, utilization, and transplant outcomes of family-directed cord blood of patients with sickle cell disease. This study was driven, at least in part, by the cost and technical challenges of

collecting and storing units. Free cord blood banking in public cord banks was offered to women who had previously delivered a child with sickle cell disease. Despite being a public bank, cords were reserved for the use of that family. All cords were stored and HLA-testing was not done (due to cost) unless requested by treating physician. Data were collected retrospectively from the cord blood bank, Eurocord registry and hospital patient records.

338 units were collected from 302 families. 28 units were used for transplantation, giving a utilization rate of 8% over 20 years. Interestingly, one center accounted for 41% of all cords banked, and utilization of 25/28 cords. This suggests that close collaboration with transplant teams is likely to increase cord blood use. There was a 96% engraftment rate and 100% survival, with all patients achieving a minimum of 80% donor chimerism. 5/28 patients had Gr.II-IV aGvHD requiring steroids. There id no data reported on cost of cord blood banking. This is a significant omission in discussing publicly funded cord banking, particularly in light of low utilization rates.

❖ HLA-matched family donor CBT results in good outcomes in patients with SCD. However, utilization rates remain low and data on cost of publicly funding such banks is not available.

Bleeding risk of surgery and its prevention in patients with inherited platelet disorders

Orsini, S et al, 2017, Hematologica

Inherited platelet disorders are a heterogenous group of diseases with a wide spectrum of clinical severity. Individually, they are rare and thus challenging to study. As such, the majority of data available is from small studies and guidelines are based on expert opinion. This paper was a retrospective study aimed at evaluating the bleeding complications associated with surgical procedures in all inherited platelet disorders. This was a multi-center, retrospective cohort study by the Scientific Working Group on Thrombocytopenias and Platelet Function Disorders of the European Hematology Association. Participating centers were asked to review records of patients with inherited bleeding disorders that underwent surgical procedures. Patients were divided into those with platelet number disorders (IPND) and those with platelet function disorders (IPFD). Data on procedures, bleeding, and use of prophylactic regimens were collected.

There were 423 patients and 829 procedures in total. Baseline bleeding scores were higher for patients with IPFD and these patients were twice as likely to have excessive bleeding after surgery as compared to patients with IPND (25% compared to 13%). Cardiovascular and urologic surgery were associated with an increased likelihood of bleeding, while the use of pre-operative pro-hemostatic agents was associated with less bleeding. ddAVP with or without anti-fibrinolytic agents was found to be the preventative treatment associated with the lowest bleeding rate. For patients with IPND, a platelet count below 68 was found to be the cut-off under which bleeding rate increased significantly.

There are numerous limitations to this study: Firstly, it is retrospective and relies on the survey filled by participating centres. It also included patient/family responses mixed in with data from medical records. Second, given the rarity of many of platelet disorders, the cohort is heavily influenced by a subset of diagnoses. While the authors make attempts to do sub-analyses, there are insufficient data to make reasonable conclusions. Third, the decision to use prophylaxis and choice of agents used was entirely dependent on the treating physician. Fourth, the authors conclusions that ddAVP and anti-fibrinolytic therapy is the most efficacious therapy for IPFD is misleading. As this was the most commonly used therapy for IPFD with a milder bleeding phenotype, it is not surprising that it was efficacious. Clearly, it would not be advisable as the only pro-hemostatic therapy for an IPFD with a severe bleeding phenotype, such as Glanzmann Thrombasthenia or another where the underlying hemostatic defect in not affected by ddAVP. Fifth, they do not provide any data on complications of using prophylaxis (ex. thrombosis with rFVIIa).

❖ This paper supports previous anecdotal data and expert-derived guidelines: Patients with inherited platelet function disorders bleed more than those with thrombocytopenias. Patients with a history of bleeding are more likely to have severe bleeding. Use of pre-operative prophylaxis reduces surgical bleeding. There is insufficient evidence to recommend specific interventions to minimize bleeding in these patients.

Section 2. Leukemia and Lymphoma & Bone Marrow Transplantation

Improved outcomes for myeloid leukemia of Down syndrome: a report from the Children's Oncology Group AAML0431 trial

Taub, JW et al, 2017, Blood

Children with Down syndrome have an increased risk of myeloid leukemia (ML), which generally has unique features such as a megakaryoblastic subtype, preceding transient abnormal myelopoiesis, and association with mutations in the GATA1 transcription factor. Many have a myelodysplastic phase that precedes the development of AML. Excellent cure rates have been achieved, but excessive deaths have been observed due to infection and cardiac dysfunction. The Children's Oncology Group study aimed to adapt therapy for Down syndrome ML to capitalize on the sensitive of blasts to cytarabine (ARAC) and daunorubicin with more effective use of high-dose ARAC and reduced daunorubicin dosing. In the treatment protocol, high-dose ARAC was used earlier in the second induction cycle instead of daunorubicin, resulting in a 25% lower cumulative dose. Minimal residual disease (MRD) testing was performed as an optional biology study.

205 children were enrolled, with a 5-year OS of 93% and EFS of 89.9%. Kaplan-Meier curves demonstrated improved outcomes compared to historical controls for all patients, with statistically significant p-values. MRD showed worse outcomes for those patients with increased levels at the end of the first induction cycle. Toxicity was noted to be highest with the high-dose ARAC in Induction block II, accounting for two-thirds of all grade 3 or higher adverse events. While outcomes were compared to historical controls, there was no corresponding analysis for toxicity. Although the authors speculated as to the impact of myelosuppression related to the high-dose ARAC, it is difficult to conclude whether the toxicity seen is a significant or important change.

❖ Reduction in daunorubicin and changes in the administration of ARAC were associated with improved EFS and OS in patients with Down syndrome and ML. MRD at the end of Induction I was the only significant predictor of outcome.

Therapy reduction in patients with Down syndrome and myeloid leukemia: the international ML-DS 2006 trial

Uffmann M et al, 2017, Blood

Children with Down syndrome have an increased risk of myeloid leukemia (ML), the majority of which show a megakaryoblastic subtype and may evolve from transient abnormal myelopoiesis. They are associated with mutations in the GATA1 transcription factor. Excellent cure rates have been achieved, felt to be due to enhanced drug sensitivity in the blasts, but treatment-related mortality remains the major cause of death. Building on a reduced intensity therapy for children with ML and Down syndrome, the treatment in this BFM trial was further intensity-reduced by excluding etoposide from the consolidation phase of therapy (450 mg/m2 cumulative dose rather than 950 mg/m2), decreased intrathecal cytarabine therapy, and the elimination of maintenance chemotherapy. The aim was to reduce treatment-related toxicity while preserving a high EFS.

170 patients were enrolled from 2006 to 2015, and had an excellent outcome with a 5-year OS of 89% and EFS of 87%. This was not significantly different than the historical control. There was no correlation of outcome noted with cytogenetic abnormalities, although poor early response to therapy (by morphologic assessment) and trisomy 8 was associated with worse prognosis. There were less infectious complications observed compared to the historical control, and the overall treatment related mortality was 2.9% compared to 5%. The authors comment that there is still no clear evidence of the role of high-dose cytarabine and anthracycline dosing in ML in Down syndrome, such that the approach to risk-adapted therapy used here is only one possible option.

❖ Risk-adapted therapy in myeloid leukemia associated with Down syndrome can reduce toxicity without adversely impacting outcome. Early therapy response may be predictive of treatment outcome and relapse.

Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults

Gardner, RA et al, 2017, Blood

Autologous T-cells expressing CD19-specific chimeric antigen receptor (CAR) can induce remission in B-lineage leukemias, specifically refractory ALL, regardless of disease burden. Treatment has been limited by high failure rate in CAR T-cell manufacturing, heterogeneity of response, and treatment associated toxicities. The authors developed a streamlined manufacturing process for CAR T-cells from a single apheresis product, with a defined 1:1 ratio of CD4/CD8 CAR T cells and selected for high CAR production. Cytokine cocktails were designed to produce homogeneous T-cell differentiation for engraftment fitness. Feasibility of the process, clinical efficacy, and toxicity was evaluated in 45 patients with relapsed or refractory CD19+ ALL. Patients had a varied disease burden and a variable prior treatment history, including some patients who had previously received hematopoietic stem cell transplantation or CD19 directed therapy.

The manufacturing process was highly successful (100% in minimally pretreated and 93% in heavily pretreated patients), and detectable engraftment was observed in 98% of patients at a median of 10 days. Pre-treatment lymphodepletion with both fludarabine and cyclophosphamide was more effective that cyclophosphamide alone. At a median follow up time of 9.6 months, EFS is 50.8% with OS of 69.5%. B-cell aplasia was used as a marker of functional CAR T-cell activity, and observed in 93% of patients - loss of B-cell aplasia was correlated with risk of leukemic relapse, with a hazard ratio of 34. Cytokine release syndrome and neurotoxicity were the most common adverse events, but there were no deaths from toxicity.

While the authors comment in the results about the variable success depending on the lymphodepletion regimen, the actual protocol is not specified in the Methods, nor do they explain how they determined which patients would be given fludarabine. As well, the variety of patients included support the potential role of this therapy in difficult to treat disease, but make it difficult to extrapolate recommendations for any one disease state.

❖ Manufacturing of CAR T-cells using cell purification, enriched transgene expression, and cocktails of recombinant cytokines can reproducibly produce products with therapeutic potency. The use of lymphodepletion with both fludarabine and cyclophosphamide may be associated with better persistence and effect of the CAR T-cells.

Section 3. Oncology: Solid Tumors and Neuro-Oncology

Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial

Mody, R et al, 2017, Lancet Oncology

Survival for children with high-risk neuroblastoma remains approximately 50%. Neuroblastoma cells are sensitive to mTOR inhibitors (such as temsirolimus) in vitro and in vivo. Dinutuximab is a chimeric antibody targeting GD2, which is expressed on neuroblastoma cells. This trial was designed to determine whether dinituximab or temsirolimus should be used in the next front-line trial in combination with chemotherapy. This open-label, randomized, phase 2 "pick-the-winner" COG trial (ANBL 1221) included patients of any age with neuroblastoma or ganglioneuroblastoma at first designation of relapse, progression, or refractory disease. Patients were excluded if bone marrow was the only site of disease or if they were previously treated for refractory or relapsed disease (including if they previously received irinotecan-temozolomide). Patients all received irinotecan and temozolamide with the randomized addition of either temsirolimus or dinutuximab (plus GM-CSF) in 21-day cycles up to a maximum of 17 cycles. The primary endpoint was the proportion of patients achieving an objective response (complete or partial) after 6 cycles.

Between February 2013 and March 2015, 18 patients received irinotecan-temozolomide-temsirolimus and 17 patients received irinotecan-temozolomide-dinutuximab. Only 1 patient on the temsirolimus arm achieved a partial response while 9 patients on the dinutuximab arm had objective responses. In 7 of the 9 patients who responded to dinutuximab, the best response was seen after only 2 cycles. The toxicity profile of irinotecan-temozolomide-dinutuximab was manageable. Adverse events known to accompany dinutuximab (pain, fever, electrolyte abnormalities) were seen although hematological toxicity was relatively modest. Small sample size is a limitation. Only patients with first episode of relapsed or refractory disease were included, so the role of this therapy in other settings remains unclear. Overall survival may be impacted by other factors such as other therapy following the study treatment. It is unclear how many cycles therapy should be given for.

❖ Irinotecan-temozolomide-dinutuximab showed notable anti-tumor activity in patients with relapsed or refractory neuroblastoma and met criteria for selection as the combination meriting further study. ANBL1221 is an ongoing study now with a single arm but responses in the relapsed population are encouraging as an initial strategy for patients with relapsed/refractory neuroblastoma who have not previously received dinutuximab and can tolerate toxicities of therapy.

Upfront Window Vincristine/Irinotecan Treatment of High-Risk Hepatoblastoma: A Report From The Children's Oncology Group AHEP0731 Study Committee

Katzenstein, HM et al, 2017, Cancer

This original article shows the result of the AHEP0731 study conducted by the COG. This study explores the efficacy of a new chemotherapy regimen (2 cycles of VI administered in an upfront window) for high risk hepatoblastoma by assessing the response rate and the outcome. The study population included newly-diagnosed high risk hepatoblastoma. Patients received vincristine (V) on days 1 and 8 with irinotecan (I) on days 1 to 5. Response was assessed after 2 cycles and "response" was defined as either radiologic or decrease in AFP. Responders received 2 additional cycles of VI intermixed with 6 cycles of C5VD (cisplatin, 5-FU, vincristine and doxorubicin). Patients who were non-responders received 6 cycles of C5VD without further VI. Two study radiologists used RECIST criteria to determine overall response for all patients.

32 patients were enrolled. 14/30 evaluable patients were responders (RECIST and AFP in 6 patients, RECIST only in 3 patients, and AFP only in 5 patients). However, an additional group of 15 patients had some decrease in AFP (7%-89%) in response to VI. The median AFP decline after 2 cycles of VI for the entire group was 85% of the initial AFP. The 3-year event-free and overall survival rates were 49% (95% CI, 30%-65%) and 62% (95% CI, 42%-77%), respectively. Small number of patients. The way they assess their primary outcome may have impacted their ability to demonstrate the efficacy of this new regimen. This underlines the importance of using the appropriate assessment tool (any AFP decline versus a real cut-off of 90% decline).

❖ Although VI regimen did not meet predetermined criteria for demonstrating sufficient disease control, it appears to have a substantial activity in a large group of newly diagnosed patients with high-risk HB. Its role remains to be determined.

Systemic neoadjuvant chemotherapy for Group B intraocular retinoblastoma (ARET0331): A report from the Children's Oncology Group

Friedman, D et al, 2017, Pediatric Blood and Cancer

Group B retinoblastoma currently treated with systemic chemotherapy (carboplatin, vincristine, etoposide) and local ophthalmic therapies with the goal of avoiding enucleation and external beam radiation and the long term morbidity and mortality associated with these therapies. However, patients still exposed to etoposide thus concerns about secondary leukemia. Goal of this study was to demonstrate that the removal of etoposide would not significantly alter EFS.Multicentre, single arm trial comparing the 2-year EFS of vincristine and carboplatin compared to the historical 2-year EFS of 96% with 3 drug therapy. Twenty-one patients (25 eyes) were treated with six cycles of VC, accompanied by local ophthalmic therapies after cycle 1. All examinations under anaesthesia were reviewed centrally to confirm group B retinoblastoma.

All patients had tumor regression after the first cycle of VC and only two patients had progression during therapy. There were seven treatment failures resulting in a 2-year EFS of 65% and early study closure in accordance with the statistical design. All treatment failures were local and salvaged with additional therapy (OS 100%). The 2-year cumulative incidence of enucleation and radiation therapy was 15% and 10% respectively. Suggested explanations for altered EFS were removal of etoposide, multicentre study (instead of single institution w/ significant retinoblastoma expertise), or due to delay of local ophthalmic therapy until after cycle 1. Single arm study of small cohort with short follow up.

❖ Removal of etoposide in treatment of Group B intraocular retinoblastoma resulted in worse EFS compared to 3 drugs, however OS was 100%.

Surgery alone is sufficient therapy for children and adolescents with low-risk synovial sarcoma: A joint analysis from the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group

Ferrari, A et al, 2017, European Journal of Cancer

Approaches to synovial sarcomas (SS) have involved multimodal therapy using chemotherapy, surgery and radiation therapy. Retrospective analysis has suggested that low-risk SS may be treated with surgery alone. European and North American clinical trials in Non-rhabdomyosarcoma soft tissue sarcoma used a risk-based approach to therapy. This analysis reports on the pooled the data from the European (EpSSG NRSTS 2005) and North American (COG ARST0332) sarcoma trials.

Subset analysis of prospective study: 60 patients with synovial sarcoma under age 21 enrolled on European paediatric Soft tissue sarcoma Study Group (N=24) and Children Oncology Group (COG) trials (N=36), who had received surgery alone with complete resection. Median tumor size was 3 cm. 3-year EFS was 90% (82%, 98%), OS 100%. 8 local tumor recurrences; all were salvaged with combinations of surgery, chemotherapy and/or radiation therapy. Small tumor size = 3cm was predictive of EFS but clinical trial approach, age, gender, grade and site did not predict EFS. Difference in patients eligible for surgery-only approach for SS patients in different trials. Limited number patients with large tumors.

❖ This study showed that small synovial sarcomas ≤ 5cm that are completely resected with negative margins can be treated with surgery alone.

Treatment pathway of bone sarcoma in children, adolescents, and young adults

Reed, DR et al, 2017, Cancer

This review presents a pathway through different types of management of bone sarcomas in children, adolescents, and young adults.

Desmoid Tumors and Celecoxib with Sorafenib

Benech, N et al2017, New England Journal of Medicine

2 case reports of adults with FAP and refractory abdominal desmoid tumors with long term response to a combination of celecoxib and sorafenib.

❖ A potential new treatment for a difficult disease - may only be applicable in patients with FAP. If feasible, larger clinical trials would provide better data.

Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors

Ramkissoon, SH et al, 2017, Neuro-Oncology

Sub-type specific mutations have been identified in many pediatric brain tumors, and are critical to developing and initiating targeted therapy. This report from Boston describes their experience in pediatric neuro-oncology with targeted exome sequencing and genome-wide copy number analysis of the tumour using a CLIA approved test. Clinical data was extracted from the chart and histology was reviewed. OncoPanel was used for targeted exome sequencing (surveys 300 cancer genes) and classified into 4 tiers (Tier 1 is a well described mutation with evidence confirming clinical utility). Clinical array comparative genomic hybridization (aCGH) was used to identify copy number alterations, known as OncoCopy. Whole genome sequencing was also done. Medulloblastomas underwent further DNA-based molecular analysis to determine subgroup.

OncoPanel was requested on 142 tumors and clinical data was available on 120 of these patients. OncoCopy was requested with results available on 146 patients during time of study. Sixty patients had both tests performed. Clustering of copy number variations was shown to predict histology (i.e. HGG clustered together with embryonal tumors, LGG clustered together in a separate group, etc.). OncoPanel identified relevant alterations in 56% of patients with 38% having tier 1-3 mutations and an additional 17% having an actionable target. Eight out of 37 patients with an actionable target were treated with a small molecule inhibitor. Rearrangements (fusions) were identified in 25/115 samples, most commonly BRAF:KIAA1549 in LGGs. Novel fusions were found and verified using whole exome sequencing. There is further description regarding medulloblastoma, HGG and LGG methods and specific findings.

Germline DNA was not assessed and therefore germline variants couldn't be evaluated which would be needed to be sure about the identified variants in the tumor being somatic (arising in the tumor rather than associated with cancer predispositions). While the authors mention how many patients received targeted therapy (a small minority), they do not discuss the response of these patients to this treatment. Most of this information was not used to influence patient treatment, rather for better understanding. They do not discuss the outcomes of patients with particular alterations (i.e. BRAF V600E mutation) to learn more about how these molecular events influence response to treatment.

❖ Targeted exome sequencing and copy number alterations can be used to identify previously-known and novel mutations and fusions. This testing is already underway and offered at other institutions. This may influence if a patient may be eligible/benefit from certain phase 1 studies, but generally is not being using to guide treatment.

Maintenance therapy with everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis (the EMINENTS study)

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

Everolimus is an mTOR inhibitor which is used in the treatment of patients with tuberous sclerosis (TS), specifically those with subependymal giant cell astrocytomas (SEGAs) which cannot be curatively resected. Current protocols involve daily treatment with everolimus on an ongoing basis, though it has been hypothesized that once the disease has stabilized that the dose may

be reduced. This is an important consideration given that, while the short term side effects are considered acceptable, long term side effects of everolimus therapy remain less known. This study is a single arm prospective trial designed to evaluate the efficacy and safety of a dose reduced everolimus maintenance therapy following initial disease treatment and stabilization.

Ten patients with TS-related SEGAs were included in this trial. Following at least 12 months of treatment therapy with everolimus resulting in tumor reduction and stabilization, patients were given a reduced dose (3 doses/week rather than daily) of everolimus over the subsequent 12 months. The primary outcome was the proportion of patients with stable disease. The tumors all increased in size after reduction in therapy but the increase occurred in the first 90 days after which there was stabilization. Given the a priori criterion for progression as a 50% increase in volume, this was not considered a statistically significant difference. No recurrence of symptoms from the tumors were noted. Adverse events were less severe and less frequent with reduced treatment compared with the daily standard everolimus treatment. Limitations of this study include lack of randomization and very small patient cohort, a criterion for progression (50% tumor increase) which could be challenged, and the risk of noncompliance when the medication was only ordered for three times per week.

❖ Dose reducing everolimus in patients with TS related SEGAs following initial treatment and disease stabilization is a feasible strategy; however, further studies with larger patient cohorts should be done to confirm this finding.

A Phase II feasibility study of oral etoposide given concurrently with radiotherapy followed by dose intensive adjuvant chemotherapy for children with newly diagnosed high-risk medulloblastoma (protocol POG 9631): A report from the COG

Esbenshade, AJ, 2017, Pediatric Blood & Cancer

Standard treatment at Children's Oncology Group (COG) institutions for children over the age of 3 years with high-risk medulloblastoma currently includes craniospinal radiation with concurrent chemotherapy, followed by maintenance chemotherapy. This is a Phase II feasibility study from the COG to assess if using oral etoposide concurrently with radiation therapy could improve survival. This is a cohort study that enrolled patients with high-risk medulloblastoma. All patients underwent surgical debulking, followed by craniospinal radiation and daily oral etoposide on days 1-21 and 29-49 at 50 mg/m^2 per day. A dose limiting toxicity of dysphagia/esophagitis was noted with this dose of etoposide, and therefore the final 38 patients were treated with a lower dose of etoposide (35 mg/m^2). After radiotherapy, the patients received further maintenance chemotherapy.

This study enrolled 53 patients between the ages of 3 and 21 who had high-risk medulloblastoma between November 1998 and October 2002. There was an excellent response to the radiation and oral etoposide, with 19 (40.4%) showing a complete response, 24 (51.1%) showing a partial response and four (8.5%) with no recorded response. Overall 2 and 5 year overall survival (OS) was 80.9% and 76.6% respectively, which is comparable to previous studies. There was no significant difference in outcome between the higher and lower dose treatment groups The limitations of this study include the small size of the patient cohort, and also the lack of specific histologic or molecular stratification of tumors. This trial was also run in an era before molecular subgroups were known which limits its current generalizability.

❖ Treatment of high-risk medulloblastoma patients with oral etoposide concurrent with craniospinal radiation shows encouraging survival results when combined with standard adjuvant maintenance chemotherapy. Further studies are required to confirm effect and to identify dose-limiting toxicities. However, these studies may not be done given the current focus on treatment based on molecular subgroup.

Review of phase I and II trials for Wilms' tumour - Can we optimise the search for novel agents?

Brok, J et al, 2017, European Journal of Cancer

This is a review of 63 published phase 1 and phase 2 studies (2005-2016) which included patients with relapsed/refractory Wilms Tumors. The authors discuss availability and trial recruitment in WT, poor clinical outcome of patients, poor responses of WT to novel agents to date, and future drug development for these patients.

Biallelic TRIP13 mutations predispose to Wilms tumor and chromosome missegregation

Yost, S et al, 2017, Nature Genetics

Mosaic Variegated Aneuploidy (MVA) is a syndrome marked by constitutional aneuploidy and features of developmental delay, seizures, and - in some cases - tumor predisposition. The tumors most frequently reported in this syndrome are Wilms tumors and rhabdomyosarcomas. While some causative mutations have been identified, many cases still do not have a genetic explanation.

Whole exome sequencing (WES) of 20 families with MVA followed by targeted sequencing of TRIP13 in 12 additional children. Functional studies were done but will not be reported in this summary. WES found 6 children with MVA and biallelic TRIP13 loss of function mutations. The exact mutations were the same in each child and each of these children had a Wilms tumor. Parents of these children were heterozygous for the mutation and unaffected supporting an autosomal recessive inheritance pattern. All 3 children were of Kashmiri origin and so 11 further children with Wilms tumor (but not with known MVA) whose families originated from Kashmir were sequenced - 2 of them harbored the same biallelic TRIP 13 mutation. One of these children had other syndromic features of MVA. A sixth child with MVA and a Wilms Tumor but of Norwegian origin harbored a different biallelic loss of function mutation of TRIP13. Whole exome sequencing does not detect non-coding mutations nor copy number alterations. It is unclear why there is some variance in the phenotype in children with the same mutation.

❖ TRIP13 mutations should be considered in children with Wilms tumors and other syndromic features such as microcephaly, developmental delay, and seizures. They should be especially considered in children of Kashmiri origin.

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

Long term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: Role of chemotherapy

Teepen, JC et al, 2017, Journal of Clinical Oncology

Childhood cancer survivors (CCS) are at increased risk for secondary malignancies. Although radiotherapy is one of the major known risk factors, less is known about the impact of chemotherapeutic agents. This is a cohort study that evaluated a large Dutch population of CCS and studied their risk of developing subsequent malignant neoplasms. This study used a cohort of 6165 CCS with detailed information on individual treatments and information on subsequent malignant neoplasm follow-up. The cohort included patients treated before the age of 18 years in one of seven Dutch paediatric oncology centres between January 1st1963 and December 31st 2001. Treatment-associated risks of breast cancer, sarcoma and all solid tumours were assessed.

The median follow-up was 20.7 years since first diagnosis. The cumulative subsequent malignant neoplasm incidence at 25 years after first diagnosis was 3.9% and interestingly did not change noticeably among childhood cancer survivors treated in the 1990s compared with those treated earlier. Doxorubicin was associated with a dose dependent increased risk of female breast cancer ($p = 0.001$) whereas cyclophosphamide was associated with dose dependent increased risk of sarcoma ($p = 0.01$). The doxorubicin related breast cancer dose response was stronger in survivors with Li-Fraumeni syndrome-associated cancers suggesting a gene-anthracycline interaction in the development of breast cancer.

A limitation of the study is that despite the large size of the cohort the number of events for most of the subsequent malignant neoplasm sites was fairly low as a result of the wide age distribution at the end of the follow-up (5.3 - 65.1 years). As with other large survivorship cohorts the authors acknowledge that correlations between patient and treatment factors can potentially hamper the ability to extract meaningful information in the multivariable analysis.

❖ This study suggests that doxorubicin exposure in childhood cancer treatment is correlated with the risk of subsequent solid cancers and breast cancer whereas cyclophosphamide exposure is correlated with an increased risk of subsequent sarcomas. It is also shown in this cohort that genetic susceptibility may influence doxorubicin-associated breast cancer risk. However, it is unable to establish a causative role of these chemotherapeutic agents.

Evaluation of the need for chest X-rays in the management of asymptomatic, intraluminal vascular access device occlusion in childhood cancer

Stammers, D et al, 2017, Pediatric Blood and Cancer

Intraluminal vascular access occlusions are common complication during childhood cancer treatment. American College of Chest Physicians and the Canadian Vascular Access Association suggest that no imaging is required before thrombolysis in asymptomatic intraluminal VAD occlusion. However, some centres continue to include CXR due to concerns about administering TPA in broken or misplaced VAD and the risk of adverse bleeding events. The purpose of this research was to evaluate utility of routine CXRs prior to administering TPA for occluded VAD.

Retrospective, single centre chart review of oncology patients with line occlusions (partial or complete) leading to inability to aspirate and/or flush the line. Patients with symptomatic line occlusion (ex limb swelling) were excluded. All line occlusions were reviewed to see if CXR altered management. If so, these episodes were reviewed by a group of experts (oncologist, nurse practitioner, interventional radiologist, and thrombosis specialist) to review if administration of TPA could have resulted in harm.

85 patients experienced 123 episodes of VAD occlusion. 9 episodes of VAD occlusion were managed differently (line exchange, replace or removal) due to findings on CXR. After review by specialists only 2 episodes were thought to potentially cause harm if local TPA prior to CXR would have been instilled: port needle in wrong place and PICC broken internally. However, the paper highlights the harm would not have been life threatening. The remaining 7 episodes were lines that had migrated.

Single centre study that uses interventional radiology to place lines. Retrospective study that may have missed some episodes. The potential risk of TPA instillation was assessed in a panel review which might not reflect what truly would have happened without the CXR.

❖ This study supports the ACS statement that it is unnecessary to wait for CXR prior to local TPA administration as the CXR rarely alters management and potential harm of administering tPA in broken or misplaced line is low.

Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 Update

Lehrnbecher, T et al, 2017, The Journal of Clinical Oncology

This is an updated clinical practice guideline for the empirical management of fever and neutropenia (FN) in children with cancer and hematopoietic stem-cell transplantation recipients.

The International Pediatric Fever and Neutropenia Guideline Panel has put together this guideline (FN CPG). For questions of risk stratification and evaluation, systematic reviews of observational studies were updated. They conducted a systematic review of randomized trials of any intervention applied for the empirical management of pediatric FN. Recommendations and quality of evidence is listed throughout the manuscript.

Recommendations related to initial presentation, ongoing management, and empirical antifungal therapy of pediatric FN were reviewed; the most substantial changes were related to empirical antifungal therapy from the 2012 guideline.

Summary of the major changes from the previous 2012 guideline:
1) Peripheral blood cultures concurrently with central venous catheter cultures: quality of evidence increased to moderate from low.
2) Use of monotherapy with beta-lactam, a fourth generation cephalosporin or a carbapenem as empirical therapy in pediatric high risk FN: fourth generation cephalosporin added
3) Patients at high risk of invasive fungal disease (IFD) are those with AML, HR-ALL, or relapsing acute leukemia and children undergoing HSCT. Also those with prolonged neutropenia and high-dose corticosteroids are at high risk of IFD. All other should be categorized as IFD low-risk: risk factors refined. Quality of evidence decreased to low from moderate.
4) Consider not using serum Galactomannan (GM) : now weak recommendation against GM
5) Do not use fungal PCR testing in blood: new recommendation, poor PPV and NPV not significantly high enough to be clinically useful. PCR testing not yet standardized
6) Perform CT of the lungs for IFD work-up: quality of evidence decreased to low from moderate. Lungs are consistently the most commonly affected site. Optimal timing of initial and repeated imaging not known.
7) Consider imaging of abdomen in patients without localizing signs or symptoms of IFD: New recommendation, ideal imaging modality not known.
8) Consider not routinely performing CT of sinuses if no localizing signs or symptoms of IFD: Now weak recommendation against CT sinuses
9) In IFD low-risk patients with prolonged (greater than or equal to 96 hours) FN, consider withholding empirical antifungal therapy: now weak recommendation against empirical therapy for IFD low-risk patients.

The main research gaps are listed in Table 2 of the article and fall into 3 major categories:
1) Initial presentation: Optimal temperature threshold to define fever & new serum biomarkers as diagnostic and monitoring aids
2) Ongoing management: Timing and necessity of repeated blood cultures for persistent fever, duration of empirical antibiotics for low and high risk FN, role of providing targeted antibiotics only vs. continuing broad-spectrum coverage in patients with positive cultures who remain neutropenic , determining whether the diagnostic and therapeutic approach should differ between patients with prolonged continuous fever vs. recurrent fever during FN
3) Empirical antifungal management
Role of combination biomarkers for IFD evaluation and ongoing management , identifying novel biomarkers for IFD detection , role and timing of standard imaging on patient outcomes , efficacy and safety of pre-emptive antifungal therapy appropriate duration of empirical antifungal therapy , determining appropriate pediatric dosing for currently available

antifungal agents, and identifying novel antifungal agents for empirical therapy. Overall, Cost effectiveness of different approaches to manage pediatric FN.

❖ Key differences as summarized above from 2012 FC CPG tot he 2017 FC CPG. Implementation will be the next step. Further decision making may be further guided by cost-effectiveness studies. Individual clinician's experience will be a key influencing factors to implementation and adoption of the new FN guidelines.

International incidence of childhood cancer, 2001–10: a population-based registry study

Steliarova-Foucher, E et al, 2017, Lancet Oncology

Childhood cancer burden is unknown in many low- and middle-income countries. The International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR) have coordinated a study to publish the International Incidence of Childhood Cancer, volume 3 (IICC-3), which will include ages 0-19 (rather than 0-14 in the two previous volumes reported in 1988 and 1998).

This paper provides an overview of the incidence of malignancies and non-malignant neoplasms of the CNS in 2001-2010 for children aged 0-19, based on data collected in 153 population-based cancer registries in 62 countries. They included only registries that met standard data quality criteria and that covered the entire decade 2001-2010.

There were 385,509 incident cases in children aged 0-19 years. The overall age-standardized incidence rate was 140.6 per million person-years in children 0-14 years, which has increased from 124.0 in the 1980s, and 155.8 for aged 0-19 years. The most common were leukemia, followed by CNS tumors, and lymphomas. In children aged 15-19 years, the most common were lymphomas and the group of epithelial tumors and melanoma. Incidence rates were slightly higher in boys than girls. Incidence varied significantly between and within regions and by cancer type, sex, age, and racial and ethnic group.

The reported rates are influenced by selecting only registries with quality-assured data for the entire decade of 2001-2010. Some large registries were excluded if they didn't cover the entire decade. The non-malignant tumors in the USA were only registered from 2004 onwards and were therefore excluded. Approximately 30 cancer registries dropped out of the study. Multi-ethnic populations in Europe and Canada could not be readily studied.

❖ This epidemiological population-based registry study updates information on cancer incidence in children aged 0-14 and adds the first global overview of cancer incidence in young people aged 15-19 years. They report an increase in the incidence of neoplasms since the 1980s in children aged 0-14 years. This is a unique global source of childhood cancer incidence that can be used for research and to inform public health policy.

Article series: Special Issue: Low to middle income countries (LMIC)

Various authors, 2017, British Journal of Haematology

The Volume 177, Issue 6 of June 2017 features a series of original and review articles on treatment of malignant and non-malignant diseases in low and middle income countries.

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Woodcock, J et al, 2017, New England Journal of Medicine

Good review of basket and umbrella style clinical trials and some examples of them.

Acute Kidney Injury in Patients with Cancer

Rosner, MH et al, 2017, New England Journal of Medicine

A good review of kidney injury in patients treated for cancer - the most useful part is at the end with a review of the effects of various antineoplastic agents on the kidney.

Significant and Sustained Reduction in Chemotherapy Errors Through Improvement Science

Weiss, BD et al, 2017, Journal of Oncology Practice

Interest in reducing medical errors in hospitals has been steadily gaining momentum over the last 1-2 decades. As it relates to chemotherapy, with a narrow therapeutic index and high potential for harm, a number of large US hospitals have published on the systematic changes they have made within their departments in this regard. This is a QI publication is from the Cincinnati children's hospital, an academic institution that sees > 400 new cancer diagnoses per year and has a baseline error rate of 3.9 per 1000 chemotherapy doses and uses a completely integrated electronic health record (EPIC/BEACON). Of note, 64% of near miss errors were in prescribing and hence directly relevant to physicians.

With the launch of a chemotherapy safety working group, implementation of an additional error reporting system (to capture both near misses and errors that reached the patient) along with a daily chemotherapy safety huddle and creation of noise-reduced chemo ordering 'safety zones', they reduced their error rate by 50% (1.9/1000). This reduction in errors was sustained over time. This study was limited by its generalizability to centers that are smaller in size and do not utilize an integrated electronic health record and/or may be resource limited in other ways. There was also limited discussion on educational initiatives that were implemented for prescribers (MDs) and chemo administrators (nurses) as a result of this project.

❖ Implementing additional error surveillance systems and creating a non-punitive and transparent culture of error reporting is an effective strategy to reduce chemotherapy related errors in a large academic hospital. From an MD perspective, more work needs to be published on prescriber specific interventions that can guide educational initiatives with broad generalizability.

Mixed-Methods Study of the Impact of Chronic Patient Death on Oncologists' Personal and Professional Lives

Granek, L et al, 2017, Journal of Oncology Practice

Although it is known that oncologists experience grief when their patients die, the impact of patient death on the lives of oncologists (as it relates to burnout, compassion fatigue, and emotional response) has not been thoroughly explored in the literature. This study used mixed methods to better define the extent to which the death of their patients affects adult oncologists both personally and professionally. Researchers used semi-structured interviews (qualitative) with a group of 22 oncologists from 3 centers in Israel to explore a variety of themes around death/dying. In parallel, 79 oncologists were surveyed (quantitative) on the topic. Survey questions were designed based on previous qualitative data and literature review.

Perhaps not surprisingly, the study showed that the death of their patients had both a positive and negative influence on the lives of oncologists. Positive effects included gaining perspective and learning from each patient death and becoming a better oncologist, whereas negative effects included personality changes, weakening of personal relationships, exhaustion and burnout. Quantitative results corroborated themes arising from the interviews. It is important to note that palliative care physicians, whose practice revolves around death/dying, do not experience significant burnout. This may relate to perspective; whereas death may be perceived as a failure for oncologists, palliative care professionals view it as an opportunity for alleviating symptoms and providing support.

This study surveyed adult oncologists, who see different diagnoses and experience the death of their patients more frequently than most pediatric oncologists (mean number of deaths/month = 5). The author published similar work in pediatrics (https://www.ncbi.nlm.nih.gov/pubmed/25214471) which support the same conclusions.

❖ The data from this study support the profound impact that patient death has on oncologists, both professionally and personally and confirms that the experience in adult and pediatric oncology is similar. What is equally important is using this to start a dialogue about a need to change the culture in oncology such that the emotional impact of patient death is regularly discussed and normalized.

CCR Pediatric Oncology Series - Childhood Cancer Predisposition Guidelines

Various Authors, 2017, Clinical Cancer Research

The June and July issues of Clinical Cancer Research include a collection of articles compiling the recommendation of leading pediatric oncologists regarding screening and surveillance of childhood cancer predisposition syndromes. The manuscripts are in their entirely relevant to pediatric oncologists and freely accessible.

Association of Mortality With the Death of a Sibling in Childhood

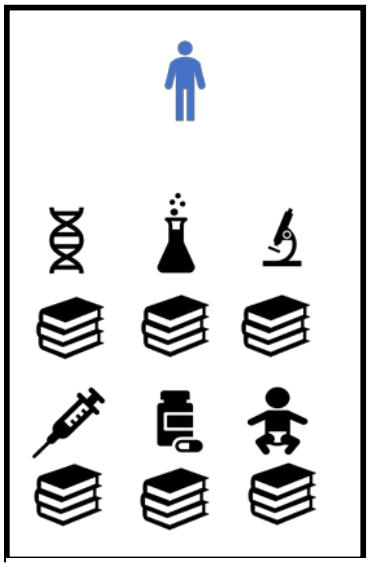
Yu, Y et al, 2017, JAMA Pediatrics

The authors investigated the association between sibling death in childhood and the mortality risk among bereaved individuals. This is a population based cohort study. Registry data was used to link live births from 1973-2004 in Denmark and from 1973-2006 in Sweden and identify the mothers and siblings. Children were placed in the exposed group if they were between 6 months to 18 years of age and had a sibling who died at any age. Children were followed until death, emigration or the end of the study. Outcomes were all-cause mortality, cause specific mortality and mortality by type of death (external causes of death or diseases).

55 818 of 5 005 029 participants experienced the death of a sibling in childhood. The median age of the bereaved siblings was 7.0 years at the time of the loss. During the follow-up period, 534 members died in the bereaved group and 25 591 died in the non-bereaved group. The bereaved group had an increase in all cause mortality when their sibling died of a disease (MRR 1.72, 95% CI 1.55-1.90) or due to an external cause (1.65, 95% CI, 1.40-1.94). Bereaved participants also had an excess of death from disease and from external cause as compared to their non-bereaved comparison. Increased mortality risks were found even after adjustment for their co-morbid diseases irrespective of the type of death of their sibling. The strongest association was found within 1 year of the sibling death. The association was also higher in same sex sibling pairs and siblings with a small age difference.

There was no data on the shared social environment of the sibling pairs or of the family environment. There may be interplay between bereavement and other factors such as social and psychological factors that may also affect the association that were not included in the data set analyzed. The study used a national data set in Denmark and Sweden and thus, results may not be generalized to all populations.

❖ Bereaved siblings who have lost a sibling during childhood have a significantly higher mortality rate than their non-bereaved counterparts in both the short and long term. Ongoing research is needed to further understand this association.



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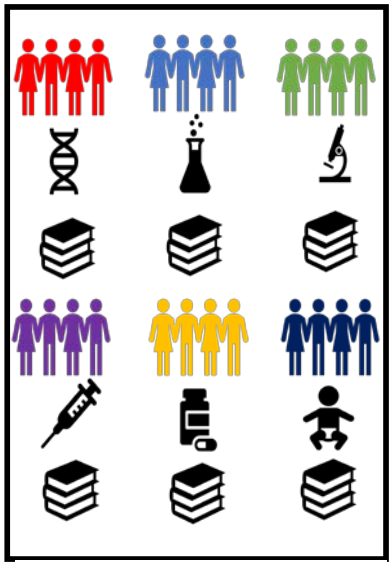

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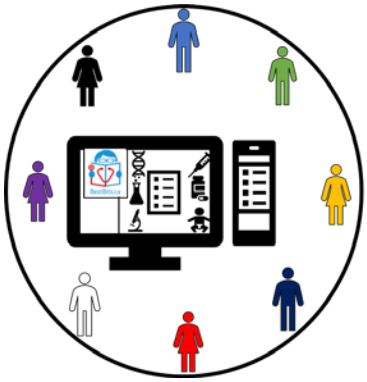

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