



January-February 2018

Issue 11

BestBits of the Pediatric Hematology Oncology literature



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Introduction

BestBits of the Literature is a synopsis of current literature in Pediatric Hematology & Oncology. The articles have been selected from clinical and scientific journals, and represent high impact research that may influence the current and future practice of pediatric hematology and oncology. Short summaries are presented with the reviewer's conclusion on the impact of the findings. All articles are posted on bestbits.ca.

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BestBits of the Pediatric Hematology Oncology Literature

Section 1. General Hematology, Thrombosis & Transfusion Medicine

Timing and severity of inhibitor development in recombinant versus plasma-derived factor VIII concentrates: a SIPPET analysis

Peyvandi, F et al, 2018, Journal of Thrombosis and Haemostasis

Inhibitor development remains a significant problem in congenital hemophilia, with a multi-factorial etiology. The SIPPET trial demonstrated that the risk of inhibitors was nearly twice as high with recombinant products as compared to plasma-derived. While most inhibitors developed within the first 20 exposure days (ED), there is little data in the literature on the time course of inhibitor development.

SIPPET was a randomized trial comparing recombinant and plasma-derived (von Willebrand containing) factor replacement products for their risk of inhibitor development. This post-hoc analysis examined the results of frequent inhibitor testing done on the included patients. Inhibitors were assessed every 3-4 EDs for patients treating on demand and every 2 weeks for patients on prophylaxis, or as clinically indicated.

All inhibitors occurred within 39 ED and 90% within 20 ED (34 and 16 ED respectively for high-titre inhibitors). Inhibitors occurred earlier with recombinant products, peaked at a higher level, and persisted longer. In the first 5 EDs, the hazard ratio for recombinant products was 3.14 for all inhibitors and 4.19 for high-titre. Evaluation of the severity of the immunogenic effect also revealed an increasing hazard ratio for recombinant products with increasing Bethesda titres.

This is a post-hoc analysis of a relatively small sample pool. Because the comparison is between high-purity recombinant product and von Willebrand containing plasma derived product, the role of von Willebrand factor cannot be determined (which may be a relevant consideration in immunogenicity).

❖ The difference in immunogenicity between recombinant and plasma-derived Factor VIII products is temporal, qualitative, and quantitative.

Venous Thromboembolism in Pediatric Hematopoietic Cell Transplant: A Multicenter Cohort Study

Rangarajan, HG et al, 2018, Biology of Blood and Marrow Transplantation

This retrospective study examined the prevalence of venous thromboembolism (VTE) in pediatric patients undergoing a hematopoietic stem cell transplant. To date there has been no large retrospective study to examine both the prevalence and risk factors associated with VTE in this at-risk population.

Utilizing the pediatric health information system; a large database comprising information from 49 US pediatric tertiary care hospitals, ICD-9 codes were used to identify patients who underwent allogeneic or autologous stem cell transplant from January 2010 to September 2014. ICD-9 codes were used to identify VTE events, disease-specific indications for transplant and transplant complications including GVHD up to one-year post transplant.

4,158 eligible patients were identified that underwent a transplant. A total of 209 VTE events were identified, leading to a prevalence of 6.97%. 70% were DVTs, 13% Budd-Chiari syndrome, 9% Pulmonary embolism and 8% portal venous thrombosis. When divided between age groups, the highest prevalence was seen in those 1 month-1-year-old (12.54%) and patients older than 21 years old (10.31%). Risk factors for VTE were identified as age >13yrs old (OR 1.38; 95%CI 1.08-1.77, p0.01) and allogeneic transplant (OR 1.60; 95%CI 1.19-2.15, p0.01). Finally, patients with VTE had increased length of stay in hospital (81 vs 54 days, p0.01), a median length of stay in the intensive care unit (18 vs 12 days, p0.01) and increased 1-year mortality (13.9% vs 5.9%, p0.01).

This is a retrospective study that depends on ICD-9 coding to correctly identify patients. Certain risk factors for VTE were not analyzed in the data including inherited thrombophilias, or prior history of VTE which would have been helpful information when analyzing the results.

❖ The overall prevalence of VTE in patients undergoing hematopoietic stem cell was 6.97%, which is comparable to previous smaller pediatric studies. The identified age groups for VTE, and risk factors demonstrated by this study may increase awareness of this complication in the post-transplant period.

Predictors of remission in children with newly diagnosed immune thrombocytopenia: Data from the Intercontinental Cooperative ITP Study Group Registry II participants

Bennett, CM et al, 2018, Pediatric Blood and Cancer

Immune thrombocytopenia (ITP) in childhood spontaneously remits in up to 80% of affected children. Predictors of remission are not well understood and identifying them could be useful for treatment decisions that impact outcomes.

Data from a large prospective cohort of pediatric patients with ITP (Registry II of Intercontinental Cooperative ITP Study Group [ICIS]) was analyzed to investigate factors that might predict remission. Included children were >4 months and 20 years of age with newly diagnosed ITP based on standard criteria. Therapy was classified as no systemic pharmacologic therapy, IVIG alone, corticosteroids alone, anti-D Ig alone, IVIG, and steroids in combination, and other.

1,239 patients were analyzed, 705 had follow-up data and came from 45 different institutions. Data collected through 12 months or through 12 and 24 months. More than half of the patients had no or mild bleeding. Patients were managed with observation alone (28%), IVIG alone (25%), corticosteroids alone (13%), and anti-D Ig (3%). Remission was achieved in 419/705 (59%) at 12 months and 211/383 (55%) at 24 months. Younger age (especially patients 1 year and 1 to 6 years) was associated with highest remission rates at both 12 and 24 months. Significant bleeding at diagnosis and pharmacologic treatment at diagnosis were statistically associated with remission at both 12 and 24 months. Highest remission rate at both 12 and 24 months occurred in the group treated with combination of corticosteroids and IVIG at diagnosis (76% and 77% respectively). Gender and platelet count at diagnosis were not significantly associated with ITP remission rates. Lower platelet count at diagnosis was not predictive of remission (contrary to previous reports).

Large numbers of patients were lost to follow-up, management decisions were at the discretion of the treating provider at multiple different institutions, and other lab studies that can impact disease course (such as ANA and red cell antibodies) were not collected.

❖ Although this study found that combination treatment with IVIG and steroids may help prevent chronic disease, it would not be appropriate to recommend this upfront at this point.

BSH Guideline: management of thrombotic and haemostatic issues in paediatric malignancy.

Sibson, KR et al, 2018, British Journal of Haematology

❖ Very good guideline for the management of VTE and bleeding in pediatric malignancy.

Utility of the immature platelet fraction in pediatric immune thrombocytopenia: Differentiating from bone marrow failure and predicting bleeding risk

McDonnell, A et al, 2018, Pediatric Blood and Cancer

The immature platelet fraction (IPF) is an emerging laboratory test for measuring platelet production/turnover. It has been proposed that these immature platelets are more hemostatic and an increase in IPF more consistent with ITP, compared to BMF.

The two objectives were to examine the ability of IPF to help distinguish patients with BMF from ITP in their initial presentation of thrombocytopenia and to determine whether the IPF or AIPN could identify a subset of patients with ITP who were at increased risk of significant bleeding.

Retrospective chart review of thrombocytopenic patients, 2 months – 21 years old, with platelet counts $50 \times 10^9/L$ at Children's Hospital of Philadelphia (CHOP) from November 1, 2013 to July 1, 2015. Charts reviewed for final diagnosis and bleeding symptoms. A bleeding severity score was retrospectively assigned.

272 patients were reviewed: 97 ITP, 11 BMF, 126 malignancies, 38 other. Cut-off IPF $> 5.2\%$ differentiated ITP from BMF with 93% sensitivity and 91% specificity. Absolute immature platelet number differed in all three bleeding severity groups (mild, moderate, severe). On multivariate analysis, an IPF 10.4% was confirmed as an independent predictor of bleeding risk at platelet counts $10 \times 10^9/l$ in patients with ITP.

Single centre, retrospective, chart review (bleeding symptoms collected based on what was documented in chart), management of ITP not standardized (physician dependent if treatment provided or not thus potentially influencing bleeding symptoms), no blinding when assigning bleeding scores.

❖ IPF measurement may have utility in diagnosis of ITP. In addition, IPF may be useful for prediction of relative future risk of bleeding in ITP patients, however there are limitations with the bleeding scores in this study.

Section 2. Leukemia, Lymphoma & Bone Marrow Transplantation

Reduced-Intensity Delayed Intensification in Standard-Risk Pediatric Acute Lymphoblastic Leukemia Defined by Undetectable Minimal Residual Disease: Results of an International Randomized Trial (AIEOP-BFM ALL 2000)

Schrappé, M et al, 2018, Journal of Clinical Oncology

Delayed intensification (DI) in acute lymphoblastic leukemia (ALL) is an essential element in treatment protocols but is intensive and associated with toxicity. This study originated from the AIEOP-BFM 2000 trial and aimed at testing non-inferiority of reduction in DI from 49 days (P-II) to 29 days (P-III) with a shorter duration of steroids and lower doses of cyclophosphamide, vincristine, and doxorubicin.

The randomized prospective trial AIEOP-BFM ALL 2000 is a European multinational cohort study. From 2000 to 2006, 4,937 patients were enrolled on the trial. Of 1,346 patients with standard risk criteria (SR, the lowest risk category), 1,164 were randomly assigned on the reduced regimen P-III or the standard regimen P-II (roughly half in each arm).

Median follow-up time was 8.4 years. The disease-free survival was 91.8% vs. 95.8% with the reduced regimen vs. the standard treatment with 62 versus 42 events ($p=0.04$). 8-year OS was 96.1% versus 98% (NS). Acute toxicity was about the same in the two regimens with slightly more life-threatening events occurring with standard therapy P-II ($n=10$ vs. 7). The reduced regimen P-III was not associated with similar outcomes compared to the standard regimen P-II and therefore, treatment reduction in SR patients with ALL was not successful in this trial. The only subgroups with similar outcomes were ETV6-RUNX1 positive ALL and patients aged 1 to 6 years. The results of this trial are specific to the BFM backbone and risk stratification which differs compared to other large international trials.

❖ Treatment reduction in delayed intensification was not successful in this trial for Standard risk ALL patients. ETV6-RUNX1 status was added as a favorable cytogenetic marker in the AIEOP-BFM 2009 trial. The 2009 trial will ask whether a reduction of the 4-drug induction by using half the daunorubicin dose in low-risk patients leads to comparable outcomes.

Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia

O'Connor D et al, 2018, Journal of Clinical Oncology

Cytogenetic analysis and minimal residual disease (MRD) assessment are used to personalize treatment in current protocols for acute lymphoblastic leukemia (ALL). MRD status is currently assigned using cut-off limits in treatment protocols. This study assessed MRD as a continuous variable using PCR-based MRD assessment (Ig/TCR rearrangements) and correlated results with somatic genetic changes.

3,113 consecutive patients with ALL treated in the MRC UKALL2003 protocol (2003 to 2011) were eligible and 2,542 were analysed. Patients were classified into four mutually exclusive cytogenetic genetic groups: good risk: ETV6-RUNX1, high hyperdiploidy (51 to 65 chromosomes); high-risk: KMT2A (MLL) fusions, near haploidy, low hypodiploidy (40 chromosomes), iAMP21, and TCF3-HLF; intermediate risk: TCF3-PBX1 and all other patient-cases with B-ALL; and patients with T-ALL. MRD at end of induction was assessed as a continuous variable with a minimum detection level of 1×10^{-5} .

MRD results were highly dependent on genetic risk groups with ETV6-RUNX1 but also TCF3-PBX1 showing rapid MRD-clearance (in 36% and 43% respectively). Patients with iAMP21 on the other hand had a high rate of recurrence even in those with negative MRDs. T-ALL patients more frequently had not reportable results which renders the Ig/TCR PCR-based technique less reliable for this patient group. In T-ALL, outcomes were associated with MRD-negativity or frank positivity ($\geq 5\%$) but not intermediate results. This is a post hoc analysis of MRD results and treatment was not based on these findings. The impact of continuous MRD assessment was therefore not assessed on possible treatment modifications.

❖ As previously known, PCR-based high-sensitive MRD-assessment is a powerful tool and results differ between different cytogenetic groups. The inclusion of iAMP21 as a high-risk somatic change per se was supported.

IKZF1 plus Defines a New Minimal Residual Disease-Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia.

Stanulla, M et al, 2018, Journal of Clinical Oncology

This paper from the International BFM Study Group further defines the IKZF1 gene as a very poor prognostic marker in pediatric B-cell precursor ALL. The study group looked to refine the prognostic strength of the IKZF1 deletion by looking at the effect of the co-occurring gene deletions.

The study analysed 991 patients with B-cell precursor ALL from the European group (AIEOP-BFM) trial with complete information for copy number alterations of major genes associated with outcome in ALL. There was also a smaller replication cohort of 417 patients from the same trial. The study then analysed gene combinations and evaluated patient outcomes including how gene combinations affected outcomes combined with MRD status. "IKZF1 plus" was defined as an IKZF1 deletion co-occurring with deletions in CDKN2A, CDKN2B, PAX5 or PAR1 in the absence of a deletion in the ERG gene.

The IKZF1 plus group made up of 6% of patients in the cohort of children with B-cell precursor ALL (n=63). The 5-year EFS for this IKZF1 plus group was 53% compared to 79% for those with lone IKZF1 deletions and 87% for patients who lacked the IKZF1 deletion altogether. The 5-year EFS when combining the IKZF1 plus combination with MRD was 95% for standard risk MRD versus 40% for intermediate MRD and 30% for high-risk MRD. Given differences in therapy and timing/method of MRD measurement it's not clear whether these results can be generalized to other study groups.

❖ The use of the IKZF1 deletion in combination with specific additional single gene deletions, the so-called IKZF1 plus, provides an independent and strong molecular stratification marker in addition to MRD measurements. The IKZF1 plus group with positive MRD are a particularly high-risk group and should be assigned additional/experimental treatments, which will be evaluated in the upcoming AIEOP-BFM ALL 2017 trial. On the other hand, the IKZF1 plus genotype loses prognostic significance when MRD is negative.

Oncogenic mutations combined with MRD improve outcome prediction in pediatric T-cell ALL

Petit, A et al, 2018, Blood

Risk stratification for pediatric T-ALL is based primarily on clinical findings and MRD. This study aimed to identify new genetic prognostic factors to improve the detection of patients at risk of relapse. Mutations in the Notch1 and Ras pathway were selected based on their recognition as oncogenic pathways in T-ALL and the reports in adult literature demonstrating their prognostic value.

220 patients treated prospectively on the FRALLE 2000T study (France) from 2000 to 2010 who had DNA material available were retrospectively analyzed for mutations in Notch1 (N), FBXW7 (F), K-RAS/N-RAS (R) and PTEN (P), both somatic and germline. The low-risk group was defined as having N/F mutations in the absence of R/P mutations. High-risk group was defined as having both N/F and R/P somatic mutations or either N/F germline or R/P germline mutations. Multi-variable regression analyses were performed to assess whether this classification of patients into low (n=111) and high-risk (n=109) groups was prognostic. Of note, on the FRALLE 2000T study, risk stratification was based on MRD.

Classification into low-risk and high-risk genetic groups was an independent prognostic risk factor. 5-year cumulative incidences of relapse were 11% and 36% for low-risk and high-risk groups respectively. When combined with WBC count and MRD, genetic risk groups helped further identify patients at low and high risk of relapse: Patients with a WBC > 200,000/ μ L, high-risk genetics and MRD > 1×10^4 had a cumulative incidence of relapse of 46% as compared to only 2% for patients with a WBC 200,000/ μ L, low-risk genetics and MRD 1×10^4 . Retrospective analysis of a prospective cohort. Similar study based on UK2003 study did not demonstrate significance of K/N-ras and PTEN mutations.

❖ The combination of white cell count > 200,000/ μ L, MRD positivity, and genetic risk group were helpful in stratifying relapse risk in pediatric T-ALL, in particular identifying the low-risk group, in this cohort. These findings contrast with findings from the UKALL2003 data which did not find genetic risk factors contributory.

Young Female Donors Do Not Increase the Risk of Graft-versus-Host Disease or Impact Overall Outcomes in Pediatric HLA-Matched Sibling Hematopoietic Stem Cell Transplantation.

Friedrich, P et al, 2018, *Biology of Blood and Marrow Transplantation*

This is a retrospective cohort study, in 244 pediatric patients, to address the hypothesis that the presence of T and B cells sensitized by exposures during pregnancy are a contributing factor to differences in outcomes between sex-matched and sex-mismatched transplants. Theoretically, there should be no such difference when a non-exposed (non-alloimmunized) female donor is used. In the study, they assume that young (12 years) female donors are a sexually naïve population and therefore the presence of alloimmunization including to H-Y antigens should be minimal.

Data from 244 pediatric patients were analyzed. The outcome was the development of acute grade II to IV GVHD and Chronic GVHD. Survival analysis was assessed at 100 days, 1 year and 5 years. Age was dichotomized to improve the interpretability of the results. Donor age >12 yrs. represents 50% of the population in the study. Univariate analysis revealed older patient age, older donor age, conditioning with CY-TBI and earlier year of transplant as significant predictor of aGVHD. Of these, all but donor age showed significance in multivariate analysis.

The effect of female donor sex on cGVHD noted in the model adjusted for patient age, HLA match, and stem cell source lost significance if the donor was 12 years old, but increased in magnitude and was significant if the donor was ≥12 years old (OR, 13.6; 95% CI, 2.8 to 39.6). Patient age was not a significant risk factor in multivariate analyses. Population sample inclusion criteria did not consider important factors as: donor history of blood transfusions and the wide age range of participants. Age was used as a surrogate for sexual-naivety and therefore it does not directly answer the question.

❖ The study concluded that when selecting among sibling donors for a pediatric patient, priority should be given to donors 12 years of age or younger and that selection can be done independently of donor gender and sex match. Other explanations for the results of this study cannot be excluded and many limitations on patient enrolment criteria, age, and confounding factors could have impacted the results.

Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial

O'Connor, OA et al, 2018, *Lancet Oncology*

The objective of this study was to explore the safety and clinical activity of brentuximab vedotin plus bendamustine in heavily pretreated patients with relapsed or refractory Hodgkin's lymphoma and anaplastic large T-cell lymphoma. This was an international, multicentre, single-arm, phase 1-2 trial. Patients with Hodgkin's lymphoma or anaplastic large-T-cell lymphoma who had received at least one previous multi-agent chemotherapy regimen.

The trial occurred in 2 phases: Phase 1: patients were assigned following a 3+3 dose-escalation design to one of four cohorts to receive brentuximab on day 1 of a 21-day cycle and bendamustine on days 1 and 2 of a 21-day cycle. Outcomes were maximum tolerated dose and dose limiting toxicity. Phase 2: all patients received brentuximab plus bendamustine at the recommended dose from phase 1. Complete response was defined as PET negativity.

65 patients were enrolled, most with Hodgkin's lymphoma (n=64). The age range of patients was 18-72 years. 28 patients were evaluated in the phase 1 study and 37 patients were evaluated in the phase 2 study. Maximum tolerated doses were not reached. Dose limiting toxicities included grade 4 neutropenia and diffuse rash. The dose used for phase 2 was the standard dose of each agent when used independently. An overall response was achieved in 29/37 (78%) of patients. Complete response was obtained in 16/37 patients (43%).

6 patients in the phase 1 study and 3 patients in the phase 2 study had progression of disease during treatment (9/65, 14%). This was a non-randomized trial in a heavily pre-treated group of patients. There are only few patients included in this study. Only adults participated in this study with a range of ages from 18-72 years.

❖ Brentuximab vedotin and bendamustine achieved a clinical response in relapsed and refractory adult patients with Hodgkin's disease.

Value of flow cytometric analysis of peripheral blood samples in children diagnosed with acute lymphoblastic leukemia

Lam, G et al, 2018, Pediatric Blood and Cancer

Peripheral blood samples are frequently screened by flow cytometry before bone marrow for suspected leukemia to facilitate treatment decisions. Criteria to establish the diagnosis of a lymphoblastic malignancy from peripheral blood are not well defined.

Retrospective comparison of paired results of peripheral blood flow cytometry and bone marrow in 383 children with ALL diagnosed consecutively at a single center from January 2007 to February 2016. Patients were aged 0-18 years and had an adequate peripheral blood sample collected up to 7 days prior to the BMA. Four-color flow cytometry was used until September 22, 2014, then a 10-color panel was established thereafter.

Of 383 patients with B or T precursor ALL and paired results, only 3 patients had discordant results. There were 2 false positives peripheral blood samples (corresponding to lymphoblastic lymphoma with BM involvement below the threshold of leukemia and ALL that initially did not meet diagnostic criteria but later progressed) and one false negative (qualitatively positive upon review). In 75% of patients (289/383) who underwent both peripheral blood flow cytometry and BMA, the diagnostic LP and first dose of IT chemo were performed during the same sedation as the BMA. Hematopathologist experience may lead to bias.

❖ High concordance of results between peripheral blood and bone marrow flow cytometry in diagnosis of ALL. 1% or more blasts in the peripheral blood anticipated a diagnosis of ALL in the subsequent BMA with high sensitivity and specificity. Peripheral blood should not replace bone marrow in the diagnosis of ALL but integration into diagnostic approach could help with scheduling initial procedures, reduce anesthesia procedures, and optimize use of healthcare resources.

Section 3. Oncology: Solid Tumors and Neuro-Oncology

Outcome and Prognostic Factors in Stage III Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group Study AREN0532

Fernandez, CV et al, 2018, Journal of Clinical Oncology

This is a report on the outcomes of children with stage III favorable-histology Wilms tumours treated on the most recently closed COG trial AREN0532. The goal of the prospective therapeutic cohort trial was to identify clinical and biologic variables that affect the prognosis of patients with stage III favorable-histology Wilms tumor, as well as to maintain an EFS >85% and OS >95%.

588 children with stage III disease were included whether they had upfront nephrectomy or delayed nephrectomy. Any children with evidence of metastases or with LOH of 1p AND 16q or with anaplastic histology were excluded. This was a single-arm trial with central review of imaging and pathology. All children received Regimen DD4A (vincristine, doxorubicin, and dactinomycin) as well as flank or abdominal radiation depending on the local extent of disease.

Overall 4-yr EFS was 88% and 4-yr OS was 97%. Both were improved from NWTSS5, the last published North American Wilms tumor trial; 116/535 children had neoadjuvant chemotherapy; 7 children with neoadjuvant chemotherapy had completely necrotic disease - none relapsed; 7 children with neoadjuvant chemotherapy had blastemal-predominant disease - five relapsed. A combination of positive lymph nodes and LOH of 1p OR 16q conferred worse outcome. Conversely, children without nodal metastases and no LOH of 1p or 16q had exceptionally good outcomes. Most relapses occurred early (within 2 years of diagnosis) and the majority were metastatic relapses.

This was a single-arm observational trial so comparisons to other outcomes are difficult. It is especially difficult to compare to SIOP outcomes even in children who received neoadjuvant chemotherapy because the radiation doses were different and some parts of the chemotherapy regimens differed as well. Children with high-risk post-operative histology (i.e. blastemal predominance) did not have their therapy intensified unlike in SIOP. There is also likely stage migration affecting the results of this trial as all patients with lung nodules on CT and those with LOH of 1p AND 16q were excluded in this trial but not from NWTSS5. There was a trend noted toward a higher rate of delayed nephrectomy, resulting in some patients who may have had stage I or II disease being upstaged due to biopsy.

❖ There were overall good outcomes using the AREN0532 protocol of DD4A with radiation therapy, including EFS 88% and OS 97%. DD4A chemotherapy and 10-11 Gy of flank/abdo radiation after upfront nephrectomy is still the standard of care for stage III disease in North America. However, this trial indicates that there is no difference in outcome if neoadjuvant chemotherapy is used and so this is a viable option for surgically difficult cases. New risk groups may have also been identified based on lymph node metastases and LOH of a single chromosome. In particular, the group with no nodal metastases and no LOH may be able to have a reduction in therapy. Finally, all clinicians treating Wilms tumours should carefully consider intensification of therapy in cases of blastemal-predominance.

Rhabdomyosarcoma, Ewing Sarcoma, and Other Round Cell Sarcomas

Pappo, AS et al, 2018, Journal of Clinical Oncology

❖ This is a review article and part of a special JCO edition on sarcomas (January 2018, number 2) looking at genomics and potential therapeutic targets.

Osteosarcoma, Chondrosarcoma, and Chordoma

Whelan, JS et al, 2018, Journal of Clinical Oncology

❖ As part of a special edition on sarcomas in the January edition Number 2, this review article covers osteosarcoma, chondrosarcoma, and chordoma.

Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children

Drilon, A et al, 2018, New England Journal of Medicine

Fusions involving the NTRK genes have been reported in a number of different cancers and are driver events when they occur. The fusions lead to a constitutively activated tyrosine kinase that acts through the classically proliferative MAP/ERK and PI3K pathways. The fusions occur rarely in some common cancers but much more frequently in a few rare tumors including infantile fibrosarcoma, salivary gland carcinoma, and secretory breast carcinoma. This is a phase 1/2 trial of Larotrectinib - a selective inhibitor of TRK proteins.

A phase 1 trial of children and adults and a phase 2 trial of adults are both included in this publication. An ongoing phase 2 trial including children will be reported elsewhere. These single-arm trials gave either liquid or pill forms of Larotrectinib to patients on an ongoing basis until they reached a dose-limiting toxicity or had progression. Primary outcome was overall response rate by RECIST criteria.

55 patients were treated including 12 patients under 15 years of age (all children had infantile fibrosarcoma or other soft tissue sarcomas). Of all patients, the overall response rate was 75% and after a median of 9 months follow up, 86% of responders had undergone definitive surgery or continued to take Larotrectinib. Toxicity profile was limited with no DLTs and the most common grade 3/4 adverse event being increased liver enzymes, anemia, and fever. In a secondary analysis, the authors sequenced the NTRK gene in patients with drug resistance and found mutations that would likely inhibit Larotrectinib binding. Although this is a phase I/II study, patients were selected for their good performance score, and the excellent results here mean that this drug will receive approval without a phase III study.

❖ This is an effective drug for the small number of patients with NTRK fusions. This study is actually a poster child of how rare tumors can become attractive for pharmaceutical development if they are included in so-called basket trials. A larger societal limitation is the cost of sequencing all tumors. If NTRK fusions are found rarely in some common cancers (such as melanoma or colon cancer) then how many patients need to have expensive screening in order to find one patient who qualifies for what will likely be an exorbitantly expensive drug? Who will cover the costs and how do we ensure equal access?

Neuroblastoma Patients' KIR and KIR-Ligand Genotypes Influence Clinical Outcome for Dinutuximab-based Immunotherapy: A Report from the Children's Oncology Group

Erbe, AK et al, 2018, Clinical Cancer Research

The use of dinutuximab-based immunotherapy has improved the outcome for patients with high-risk neuroblastoma in a phase III clinical trial (ANBL0032). Dinutuximab is an anti-GD2 monoclonal antibody whose activity is facilitated by NK cells. KIRs on NK cells highly polymorphic and, similar to HLA haplotypes, may have an effect on cellular immune response. This secondary analysis of ANBL0032 data investigated the association between KIR/KIR-ligand genotypes and clinical outcome in high risk neuroblastoma patients randomized to immunotherapy or no immunotherapy.

A total of 226 high-risk neuroblastoma patients were enrolled into ANBL0032 in 2010 and were randomized to immunotherapy or no immunotherapy; 176 patients had DNA available for genotyping for KIR/KIR-ligands (88 immunotherapy; 86 patients no immunotherapy).

Patients with the KIR/KIR-ligand genotypes "all KIR-ligands present", "inhibitory KIR2DL2", and "inhibitory KIR3DL1" were associated with improved event-free and overall survival with >5 years follow-up if patients had received immunotherapy versus no immunotherapy. The "complementary KIR/KIR-ligand" genotypes did not improve outcome in patients receiving immunotherapy compared to isotretinoin alone.

Prior studies on KIR/KIR-ligand genotyping showed conflicting results on the benefit of different KIR/KIR-ligand genotypes on outcome in neuroblastoma, therefore validation by independent clinical studies is needed.

❖ High-risk neuroblastoma patients with certain KIR/KIR-ligand genotypes benefited from immunotherapy in this study. Validation of these findings is necessary, before KIR/KIR ligand genotyping might help to stratify future patients to immunotherapy treatment and avoid toxic side effects in patients who might not benefit from immunotherapy.

Phase II, Open Label Randomized, Multicenter Trial (HERBY) of Bevacizumab in Paediatric Patients with newly diagnosed high-grade glioma

Grill, J et al, 2018, Journal of Clinical Oncology

This paper presents the results of the HERBY study – a Phase II, randomized multicentre trial adding bevacizumab to temozolomide and radiotherapy in pediatric patients with high-grade gliomas. This trial was spurred by the success of bevacizumab in adult HGG. This was a multi-center randomized trial comparing the two treatment regimes. The primary end-point was EFS (progression, recurrence, or death) as assessed by central radiology review blinded to the treatment that the patient received.

121 patients were enrolled. The EFS did not differ significantly between the two treatment groups (Radiotherapy and temozolomide 11.8 months, Radiotherapy and temozolomide plus bevacizumab 8.2 months, $p = 0.13$). In overall survival adding bevacizumab did not reduce the risk of death. Death occurred in 28 patients (50%) in the radiotherapy and temozolomide group and 33 patients (55%) radiotherapy and temozolomide plus bevacizumab group.

Importantly there were more serious adverse events in the bevacizumab group compared to the radiotherapy and temozolomide group without bevacizumab. The trial wasn't powered to detect an effect in genetically-defined subgroups such as in tumors with histone mutations.

❖ Adding bevacizumab to radiotherapy and temozolomide did not improve EFS in pediatric patients with high-grade glioma. This is disappointing and different from the experience in previously reported adult trials using bevacizumab in adult high-grade glioma. This highlights the biological difference between adult and pediatric gliomas and the importance of conducting pediatric specific studies.

A pediatric brain tumor consortium phase II trial of capecitabine rapidly disintegrating tablets with concomitant radiation therapy in children with newly diagnosed diffuse intrinsic pontine gliomas

Kilburn, L et al, 2018, Pediatric Blood and Cancer

Outcome for children with diffuse intrinsic pontine gliomas (DIPG) remains dismal. Radiation has been shown to increase the pharmacodynamic effect of capecitabine. The primary aim of this study was to estimate PFS for children with DIPG treated with combination of capecitabine and RT.

Children 3-17 years of age with newly diagnosed DIPG without prior experimental treatment. Histology was not required. Capecitabine was initiated within 24 hr of the initiation of RT and was administered over 20 weeks. Conventional or conformal RT was administered to all patients once daily 5 days a week in 180 cGy/day fractions to a total dose of 5,580 cGy.

Thirty-five children with DIPG, all eligible, were enrolled from February 2010 to May 2011 and combines with data from 10 patients from a phase 1 study. 25 patients completed the planned protocol. 3 withdrew from treatment. Therapy was well tolerated. There was earlier progression with the capecitabine group, with 6 and 12-month PFS of 33.7% and 7.2% compared to 54.7% and 15.6% in the historical control, respectively. There was no difference in OS. Shorter PFS hypothesized to be pseudoprogression in response to therapy. Non-randomized study, so reason for shorter PFS is unclear. Regardless, this study design remains the standard for evaluating new agents in children with DIPG since the outcomes in children with DIPG have not changed over time.

❖ This combination therapy failed to improve the outcome in children with DIPG.

Liver transplantation for primary hepatic malignancies of childhood: The UNOS experience

Hamilton, EC et al, 2018, Journal of Pediatric Surgery

Factors associated with patient and graft survival following liver transplantation for children/adolescents with primary hepatic malignancies were analysed. The aim was to identify features associated with better outcomes from transplant. The United Network for Organ Sharing (UNOS) database was reviewed which is a resource containing organ transplant data. Five-year patient and graft survival as well as independent predictors of survival were assessed.

All pediatric patients who underwent liver transplant between 1987 and 2012 were included. 574 patients were identified - the majority of whom had hepatoblastoma (HB, 70%), followed by hepatocellular carcinoma (HCC, 15%), and then other primary liver tumors (15%).

Five-year overall survival was 73% - HB did much better than HCC (76% versus 63% overall survival). In the most recent time period, 3-year survival was even better with 85% for HB. The most common cause of death was recurrent or metastatic disease in 57% of deaths. Features associated with reduced survival were higher PELD scores, hospitalization at the time of transplant, ICU at the time of transplant, and people transplanted under earlier regimes.

Large database study - difficult to identify granular details such as PRETEXT stages, changes in chemotherapy regimes, choices of transplant medications postoperatively etc. Also, no information on primary transplant or rescue transplant - potentially overall survival could be even higher for primary transplants.

❖ 76% of HB patients who undergo transplant are alive at 5 years post transplant, as are 63% of pediatric HCC patients. HCC and medical condition at the time of transplant were independent predictors of graft failure/death.

Results of methotrexate-etoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study

Gaspar, N et al, 2018, European Journal of Cancer

The article reports the outcome of patients with osteosarcoma, treated in the French OS2006 study with methotrexate, etoposide, ifosfamide pre-operatively and risk adapted chemotherapy post-operatively (M-EI for good responders, M-AP for poor responders). OS2006 was a randomized trial, exploring the effect of zoledronate on survival. The results of the randomization have previously been reported. The group now reports the survival and safety of the total study population.

The French group has previously compared methotrexate/doxorubicin to methotrexate/etoposide-ifosfamide pre-operatively. Given the comparable efficacy, M-EI has become standard of care in France. Post-operatively, patients who are high-risk (either poor responders, metastatic or unresectable) receive MAP, while low-risk patients receive M-EI. This paper reports survival results on the study population of OS2006, including patients who had refused the randomization.

Only 134/374 patients received post-operative treatment as per protocol (89/221 standard-risk patients and 45/153 high-risk). In the study population, 213/409 patients, including 187/324 with localized disease, received neither doxorubicin nor cisplatin first-line treatment (pre- or postoperatively). Median follow up was 4.8 years. The 3- and 5-year EFS were 63% (95% CI, 58-68%) and 56% (95% CI, 51-62%), respectively. The 3- and 5-year OS were 81% (77-85%) and 71% (66-76%), respectively.

The authors suggest that the chemotherapy protocol proposed had the same efficacy as MAP, but with more limited long-term side effects. Unfortunately, this is not a randomized trial and there is no comparison group, so it is not adequate to answer the question. Also, a high proportion of cases was given chemotherapy not according to the protocol. While these results are promising, the role of EI in osteosarcoma treatment remains to be clarified.

❖ Treatment of osteosarcoma patients with M-EI preoperatively and risk stratified post-operative chemotherapy (MAP for high-risk patients, or M-EI for standard-risk patients) is safe and translates to survival rates comparable to those obtained with MAP. Further, randomized trials are necessary to finally define the role of EI in the treatment of osteosarcoma (perhaps identifying groups of patients, which by age, or stage of disease, could be more likely to benefit from EI).

Intravenous immunoglobulin with prednisone and risk-adapted chemotherapy for children with opsoclonus myoclonus ataxia syndrome associated with neuroblastoma (ANBLOOP3): a randomised, open-label, phase 3 trial

de Alarcon, PA et al, 2018, Lancet Child and Adolescent health

This is the first randomized clinical trial in patients with opsoclonus-myoclonus-ataxia syndrome associated with neuroblastoma. Patients affected by OMA have an excellent prognosis for OS but face a high risk of long-term neuro-cognitive sequelae, including developmental delay, speech and language deficiencies, motor sequelae, ataxia, psychiatric symptoms. The study aims at assessing the response to treatment with prednisone and risk-adapted chemotherapy, and at understanding the role of IVIG.

This was a randomized, phase 3 trial run by the Children's Oncology Group. Children up to 8 years old, with newly diagnosed, biopsy proven neuroblastoma or ganglioneuroblastoma, with OMA were randomized to receive prednisone, risk adapted chemotherapy +/- IVIG. The randomization was stratified by risk assignment. The severity of OMA and response to treatment was evaluated using the Pike and Mitchell score.

53 patients were enrolled between 2004 and 2013. 62% were female. The response rate was 81% in the IVIG group (21 of 26 patients), and 41% (11 of 27) in the non-IVIG group (odds ratio 6.1, 95% CI 1.5–25.9, $p=0.0029$). Median follow up for patients with no progression of OMA was 6.1 years. Toxicity was acceptable, with only one death, occurring in a high-risk patient post bone marrow transplant.

The trial was designed before two important pieces of information became available in the field: 1. the efficacy of dexamethasone pulses is comparable to prednisone, but with much more limited toxicity; 2. role of rituximab in the treatment of OMA. Therefore, the results of this trial may be a bit outdated. Nevertheless, the trial answers an important question regarding the role of IVIG. The lack of information on the long term follow up and neuro-cognitive outcomes is also a limitation of the study.

❖ IVIG significantly improve the response rate in patients with OMA and neuroblastoma or ganglioneuroblastoma treated with prednisone and risk-adapted chemotherapy. Their impact on long term neurocognitive outcome, and their role in patients treated with regimens including rituximab remain unknown.

Vincristine, irinotecan, and temozolomide in children and adolescents with relapsed rhabdomyosarcoma

Setty, BA et al, 2018, Pediatric Blood and Cancer

Relapsed rhabdomyosarcoma remains a disease with dismal prognosis in need of new treatment options. The addition of temozolomide to vincristine and irinotecan (VIT) in relapsed Ewing sarcoma and in two small studies of patients with relapsed RMS showed promise with improved response rates.

This multicenter retrospective study describes the progression-free survival of 19 patients from 5 tertiary care centers with relapsed RMS who received VIT at first or subsequent relapse. It is the largest series to date of children and adolescents treated with VIT for relapsed RMS.

VIT was used as first, second, third, or fourth line of therapy. Of 19 patients with median age 8 years (range 2-17), 4 received VIT as adjuvant therapy post surgery for local control and were not included in the response analysis. Of the 15 evaluable patients, none had complete or partial response, 5 had stable disease, and 11 had progressive disease. At median follow-up of 8 months, 2 patients were alive without disease, 3 were alive with disease, and 14 patients died or progressive disease. PFS at 3 months was 23%. Small sample size, limited by quality of information documented/collected due to retrospective analysis, no central radiology/pathology review, interpatient variability in dosing of chemo, no toxicity data recorded. Physicians chose this regimen rather than randomly assigning patients to it so there may be selection bias.

❖ Best response to VIT in relapsed RMS was stable disease, achieved in a quarter of patients. It is unclear from this whether VIT is effective therapy in this disease.

Outcomes After Reirradiation for Recurrent Pediatric Intracranial Ependymoma

Tsang DS et al, 2018, International Journal of Radiation Oncology Biology Physics

This is a retrospective review of 101 children aged up to 21 years treated with repeat irradiation for recurrent ependymoma. In the setting of disease recurrence, traditional dogma is that re-irradiation can lead to toxicity. In this study, the efficacy and safety of re-irradiation for patients with recurrent ependymoma was evaluated.

Retrospective review of patients treated between 1985 and 2017. Patients with localized, intracranial ependymoma treated with surgery followed by focal irradiation were included. Patients with recurrence were treated with repeat surgery, followed by either focal repeat irradiation (for those with local recurrence) or craniospinal irradiation followed by focal boost RT (for those with any distant recurrence).

For the entire cohort, 5-year overall survival (OS) was 57% and 5-year freedom-from-progression (FFP) was 37%. Patients with distant-only failure and treated with CSI had the best outcomes, with 5-year OS and FFP of 76% and 49%, respectively.

In a multivariable analysis, male sex and anaplastic recurrence were negative prognostic factors for both OS and FFP. Again, those with distant-only failure treated with CSI had the best outcomes, with a hazard ratio (HR) of 0.4 (versus local failure treated with focal RT). Gain of chromosome 1q was associated with poorer survival in the subgroup of patients with distant failure after first RT (HR 3.5). Administering CSI as part of re-irradiation reduces distant-only failures. 10-year cumulative incidence of grade ≥ 3 radiation necrosis was low, at 7.9%.

This was a retrospective study and represents a lower level of evidence as compared with a prospective study. The study had some patients who received CSI for locally recurrent ependymoma. It is unclear why CSI was given for some cases and not for others. Association of histological grade with outcome in this study may be a proxy for underlying molecular biology. Although the authors had relatively complete data on chromosome 1q gain and C11orf95-RELA fusion, they did not have methylation data to determine if these patients had Group A or B ependymomas.

❖ Retrospective study showed re-irradiation of children with recurrent ependymoma is effective without severe toxicity, particularly those with distant failures who received CSI. Further evaluation of re-irradiation will be done in upcoming prospective studies. (St. Jude re-irradiation study for ependymoma in progress (ClinicalTrials.gov identifier NCT02125786))

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

Prediction of Ischemic Heart Disease and Stroke in Survivors of Childhood Cancer

Chow, EJ et al, 2018, Journal of Clinical Oncology

The Childhood Cancer Survivor Study (CCSS) led to the largest cancer survivor follow-up cohort. It is based on data extracted from medical records and questionnaires that were sent to childhood cancer survivors (CCS). CCS have been shown to have a >10-fold increased risk of ischemic heart disease and stroke compared with siblings. This study developed a risk-prediction model using end-of-treatment data to risk stratify CCS and externally validate the model.

This manuscript used data from the CCSS from children diagnosed between 1970 and 1986 at 26 institutions in the United States and Canada (n=13,060). A random sample of siblings (n=4,023) served as comparison cohort. Two validation datasets were used: the SJLIFE cohort from St. Jude Children's Research Hospital (led by the same team as the CCSS cohort) and the EKZ/ AMC cohort (unrelated group, n= 1,300 - 1,800 CCS). A set of variables with demographic and treatment data were tested for their association with ischemic heart disease and stroke.

Predictors of ischemic heart disease were male sex, neck or chest radiation; predictors for stroke were alkylator therapy, platinum agents, cranial and chest radiation. Two models were created: a simple model where cancer therapy-related exposures were categorized as yes or no only; and a standard model where clinical dose information was known. Risk scores were attributed and summed to create low-, moderate-, and high-risk groups. Low-risk groups had cumulative incidence risks of =15% of ischemic heart disease or stroke, respectively.

The cohorts used in this study were diagnosed three or more decades ago (training data set) or at least 15 years ago (validation data sets). Therefore, these findings might not be valid for modern treatment protocols. Particularly radiation was greatly reduced and application techniques changed within the last decades.

❖ This study quantified risk factors for ischemic heart disease and stroke after childhood cancer treatment and compiled a prediction tool which might help estimate the risk for CCS.

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Schiffer, CA et al, 2018, Journal of Clinical Oncology

❖ This is review with recommendations for platelet transfusions in oncology patients (adult and pediatric).

Cancer In The National Cancer Institute Inherited Bone Marrow Failure Syndrome Cohort After Fifteen Years Of Follow-Up

Alter, BP et al, 2018, Hematologica

This study aimed to describe the incidence and characteristics of malignancy in patients with inherited bone marrow failure syndromes over a fifteen year duration. This was a prospective cohort study conducted by the National Cancer Institute. The Inherited Bone Marrow Syndrome Cohort was opened in Jan 2002 and continues to accrue participants. This cohort enrolled patients with Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, and Shwachman-Diamond syndrome.

Patients (n=530) were enrolled in the cohort starting in 2002 with the aforementioned diagnoses of inherited bone marrow failure syndromes. Diagnosis was confirmed at the NCI. Demographic and outcome measures were then collected by parent/patient report and medical chart review. The ratio of expected to observed malignancy rates were calculated and adjusted for age, sex, race, and birth cohort.

Overall leukemia was diagnosed at an incidence of 3% with DC, FA and SDS and 0% in the cohort with DBA. DC, FA and SDS had an increased risk of ALL and AML, but odds ratios were higher for AML. Solid tumours were diagnosed at an

incidence of 5% DBA, 7% DC, 12% FA and 3% SDS. The cumulative incidence of solid tumors was close to 20% by age 65 in both DC and FA.

HSCT drastically left shifted the age of diagnosis of malignancy and increased the chances of secondary malignancy in FA (rate ratio 3.5) and DC (rate ratio 5). For Fanconi Anemia patients developed head and neck squamous cell carcinomas (HNSCC), AML, vulvar SCC and brain tumors. For DC, patients reported HNSCC, AML and NHL. In DBA, patients developed lung, colon and cervical cancers. The SDS cohort was very small (n= 35) and there were two diagnoses of AML and cervical cancer.

The increased risk of both leukemias and solid tumors in all diagnostic groups were statistically significant. This study was descriptive and therefore inferences cannot be made about the underlying causality of cancer predisposition in these syndromes. There was no analysis based on the genotype to cancer predisposition. There could have been an enrolment bias in this study, with patients with more severe disease course being more likely to agree to participate.

❖ This is the largest cohort study in terms of patient life years (enrolment and duration of study) to describe outcomes in inherited bone marrow failure syndromes. Patients with inherited bone marrow failure syndromes are at increased risk for leukemias and solid tumors. This risk is greatly increased and left shift (in terms of age of diagnosis) by bone marrow transplant, which is consistent with previously reported literature.

The specific types of malignancies are specific to the bone marrow failure syndrome and are described in this article. This is relevant to clinical practice in terms of surveillance of this patient population.

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