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BestBits of the Pediatric Hematology Oncology literature



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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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BestBits of the Pediatric Hematology Oncology Literature

Section 1. General Hematology, Thrombosis & Transfusion Medicine

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

Townsley, DM et al, 2017, The New England Journal of Medicine

For pediatric patients with a diagnosis of Aplastic Anemia and without matched-related donor, immune suppressive treatment (IST) is the treatment of choice and leads to an initial response in about 2/3 of patients with about 1/3 of initial responders relapsing over time and 10-20% developing clonal evolution. This article addresses the question whether addition of eltrombopag, an oral thrombopoietin-receptor agonist leads to an increase in response to IST. Eltrombopag was previously shown to lead to a response in a subset of IST-refractory patients with aplastic anemia, particularly in those with a higher reticulocyte count. The authors are among the most established people performing research on aplastic anemia and are affiliated to the NIH.

This is a phase I/II study with 92 patients divided into three groups with varying timing of addition of eltrombopag: either from day 14 to 6 months, from day 14 to 3 months, or from day 1 to 6 months after IST (cohorts 1, 2, and 3 respectively). The main outcome was complete response (CR) after 6 months. In this trial, the best results were seen in the group starting eltrombopag with IST and continuing to 6 months (cohort 3) with 58% CR and 94% overall response (OR). The other treatment groups led to CR of 33% and 26% (87% and 80% OR) in cohort 1 and cohort 2, respectively. This is far better than what was seen in the historical controls used in this trial with 10% CR and 66% OR.

A major limitation to this trial was that there were only historical controls and no direct comparison group without eltrombopag. The retic counts in the eltrombopag group were slightly higher compared to controls which might point towards a "milder" disease. The whole cohort consisted of a mixed group of adults and kids with a wide age range (3-82 years). Finally, there was an amendment in the middle of the study period extending the time of cyclosporine A treatment from 6 months to 24 months adding further uncertainty what caused the better response in cohort 3 which was treated last.

❖ Eltrombopag was shown to increase response rate in a mixed cohort of pediatric and adult patients when being added to IST upfront together with a prolonged duration of cyclosporine A treatment of 24 months. While these results are very promising, further data will be needed from pediatric cohorts.

Prophylaxis usage, bleeding rates, and joint outcomes of hemophilia, 1999 to 2010: a surveillance project

Manco-Johnson, M et al, 2017, Blood

Joint arthropathy in hemophilia is caused by recurrent hemorrhage into joints and ultimately may lead to destruction of the joint, chronic pain, and limited function which ultimately impacts on patient quality of life and employment. Prophylaxis has been shown to prevent joint bleeding and arthropathy. The adoption of prophylaxis in the US and Canada has increased in all age groups but generally has been greater in younger age groups compared to adults.

The Universal Data Collection (UDC) system collected predefined data from the annual visits of hemophilia patients from 134 US Hemophilia Centers. Data was analyzed in a cross-sectional manner for each study year as well as longitudinal analysis performed on data from participants who had more than 1 clinic visit during the study period. Data was collected from 6196 males with severe hemophilia A. Longitudinal data were available for 3078 participants.

Joint bleeding rates fell by 22% in prophylaxis patients during the study period. A similar decrease (23%) was noted in nonprophylaxis individuals, however the rates of joint bleed and total bleeding events were twice that of patients on prophylaxis. The number of target joints and the rate of target joint bleeding fell significantly in both prophylaxis (80% reduction) and nonprophylaxis (60% reduction) groups. Over time, joint range of motion (ROM) decreased with age regardless of prophylaxis. Decreased rate of joint ROM loss was significantly associated with primary prophylaxis institution before 4 years of age while it was increased by obesity.

The cross-sectional data could limit the conclusions regarding the association between prophylaxis use and decreased bleeding rates but the longitudinal analysis of a smaller group mitigates this weakness. In addition, bleed events were by patient self-report. Interestingly, the nonprophylaxis groups also displayed improved joint outcomes but the reasons for this are unclear - it is hypothesized that the group, over time, may have lost patients to prophylaxis, while other factors such as increased education, and effect of study surveillance may have affected the use of on-demand treatment and preventive measures in both groups.

❖ This paper shows that bleeding rates (joint and overall) have decreased with a concomitant increase in prophylaxis usage in severe hemophilia A patients in the United States between 1999 and 2010 providing further evidence supporting the use of primary prophylaxis. Still, joint range of motion was decreased over time regardless of prophylaxis which highlights room for improvement. Primary prophylaxis institution before 4 years of age was protective while obesity was associated with worse outcomes.

Modulating immunogenicity of factor IX by fusion to an immunoglobulin Fc domain: a study using a hemophilia B mouse model

Levin, D et al, 2017, Journal of Thrombosis and Hemostasis

Fusion of therapeutic molecules to the Fc domain of immunoglobulin has been used to increase plasma half-life through the neonatal Fc receptor recycling mechanism. Recently this has been used in hemophilia for Factor VIII and Factor IX (F.IX) replacement. Fc-fusion was noted to alter the development of anti-F.IX and F.IX inhibitory antibodies, although the mechanism was not clear from clinical studies.

The authors developed a F.IX fusion product with mouse Fc, to allow the evaluation of immunological response in a mouse model of hemophilia B. These mice were administered either recombinant human F.IX (hFIX), hFIX with a mouse Fc fusion (hFIX-mFc), and hFIX with a human Fc fusion (hFIX-hFc). Anti-F.IX IgG was measured, and IgE levels were also monitored. Inhibitory antibodies to F.IX were determined by a modified Bethesda assay. Cytokine and immunological (B, memory B, and T cell) repertoires were also measured from cultured splenic cells.

Mice showed a strong immunological response to hFIX-hFc, highlighting the importance of using the murine Fc in the study. Mice treated with the hFIX-mFc had higher levels of anti-F.IX IgG and inhibitory antibodies compared with only hFIX treated mice, but lower IgE titres. The authors postulated that Fc fusion modulates the T-cell response to hFIX, switching from a Th2 to a Th1 response, and further evaluated this with cytokine profiles. Further evaluation of the interaction with cell surface receptors reveal that hFIX-mFc, but not hFIX, bound specifically to Fc receptors on professional antigen presenting cells (APCs). Targeting of the F.IX antigen to these APCs allows enhanced presentation and priming of immunity, and this strong signalling may also encourage the Th1 phenotype. Because these studies were conducted in a mouse model, the extrapolation of results to humans is always uncertain. However, there is good validity and plausibility in the results.

❖ Fc-fusion to Factor IX may alter its immunogenicity, affecting both the development of inhibitory antibodies and the risk of anaphylactic reactions. If these results hold true in humans, it implies a lower risk of anaphylaxis but a higher risk of inhibitor development likely driven by a Th1 to Th2 switch.

Simvastatin reduces vaso-occlusive pain in sickle cell anaemia: a pilot efficacy trial

Hoppe, C et al, 2017, British Journal of Haematology

Vaso-occlusion crises account for the vast majority of sickle cell-related hospital admissions. The pathophysiology has been increasingly linked to inflammation which exacerbates sickling in experimental models and correlates with clinical disease severity. Statins are known to improve endothelial function independent of their lipid-lowering effects, by suppressing inflammation and restoring nitric oxide (NO) production. This study assesses the efficacy of simvastatin in reducing daily vaso-occlusive pain events in paediatric and adult patients with SCA. The study was a single centre, open label, non-

randomized trial in 19 subjects. All subjects received simvastatin in a single oral dose according to weight once daily for 3 months. The frequency and intensity of pain was measured using a daily e-diary record for 3 months of treatment with simvastatin. The total study duration with follow-up was 5 months. The adherence to treatment with simvastatin, was assessed by verbal report and monthly pill count.

Simvastatin was associated with an 85% reduction in the frequency of self-reported pain events and a parallel reduction in analgesic use. Despite the marked decline in pain rate, pain intensity did not change with simvastatin. There was also improvement in soluble biomarkers of inflammation and an acceptable safety profile. Open label non-randomized trial with a small sample size with possible selection bias. A much larger and well controlled study is needed to understand the long-term safety and efficacy of simvastatin in SCA.

❖ Simvastatin is an interesting & novel potential preventative treatment for VOC that needs further exploration before clinical use.

Safety, efficacy and pharmacokinetics of rVIII-SingleChain in children with severe hemophilia A: results of a multicenter clinical trial

Stasyshyn, O et al, 2017, Journal of Thrombosis and Hemostasis

rVIII-SingleChain is a new recombinant Factor VIII (F.VIII) molecule in which the heavy and light chains are fused to achieve a single protein, which is indistinguishable from endogenous F.VIII. It has an increased binding to von Willebrand factor (vWF) leading to a potentially increased half life and decreased risk of F.VIII inhibitors.

This prospective phase III trial recruited previously treated pediatric patients (younger than 12 years) with no personal or family history of inhibitors. They received either prophylaxis or on-demand therapy and were dosed at investigator's discretion. Efficacy and safety were regularly assessed, and inhibitor screening was performed. Pharmacokinetic evaluation was done using the chromogenic substrate assay, which has been shown to be more accurate with this molecule.

84 patients were followed across 19 countries: PK studies showed a mean half life of just over 10 hours. Efficacy was demonstrated for treatment of acute bleeds, and there were no safety concerns or development of new inhibitors. For patients on prophylaxis, the annualized bleeding rate (ABR) was 3.69, and the annualized spontaneous bleeding rate was 0. The ABR was noted to be slightly higher in the 6 to 12-year-old group, likely reflecting their increased activity. Many patients were able to decrease the frequency of their prophylactic injections, although a few required more frequent infusions. Since the treatment regimen, including dosing, was left to the discretion of the investigator, there is a significant potential for bias. It also makes it challenging to compare the ABR across the different prophylactic groups.

❖ rVIII-SingleChain is a safe and effective option for treatment of severe Hemophilia A, but it is unclear whether it offers an advantage over the other products currently available.

Genetics, diagnosis and clinical features of congenital hypodysfibrinogenemia: a systematic literature review and report of a novel mutation

Casini, A et al, 2017, Journal of Thrombosis and Hemostasis

Congenital fibrinogen disorders are usually caused by deficiency or functional defects in the molecule. Hypodysfibrinogenemia has features of both quantitative and qualitative defects, and is often misdiagnosed as simply hypofibrinogenemia. Various genetic aberrations were reported in previous publications, including heterozygosity and compound heterozygosity for nonsense and missense mutations.

The authors describe a case suggesting hypodysfibrinogenemia and leading to genetic analysis of the three fibrinogen genes (FGA, FGB, FGG). Subsequently, the authors performed a systematic review of the literature for studies of hypodysfibrinogenemia and compiled these results to identify the breadth of genetic aberrations associated with this entity.

The literature review identified 32 single mutations in 51 patients with hypodysfibrinogenemia, which were mainly missense and nonsense mutations. Compound heterozygosity for mutations known to cause both hypo- and dys-fibrinogenemia was also noted. Clinically, these patients had a wide variety of clinical symptoms, including both bleeding (45%) and thrombosis (44%). This is a systematic review of case reports and small series. While the literature search was thorough, this is a major limitation, and subject to both reporting and publication bias.

❖ Hypodysfibrinogenemia is a rare condition caused by a wide variety of molecular abnormalities and leading to a wide range of clinical presentations. Both antigenic and functional measurements of fibrinogen are necessary to ensure that it is not misdiagnosed as hypofibrinogenemia.

Thrombophilia risk is not increased in children after perinatal stroke

Curtis, C et al, 2017, Blood

Perinatal stroke is the leading cause of hemi-paretic cerebral palsy. This study aimed to prospectively identify the rates of thrombophilia in children with perinatal stroke and compare it to healthy case-controls, thus determine the need for thrombophilia testing in this population.

This was a single-center, prospective, population-based, case-control study. 135 patients with perinatal stroke were identified through the Alberta Perinatal Stroke Project registry. They were classified as having non-ischemic arterial stroke (NAIS), arterial presumed perinatal stroke (APPIS), or fetal periventricular venous infarction (PVI) based on MRI finding and absence of identifiable etiologies. These patients had thrombophilia testing at 12 months of age or at the time of presentation (if older than 12 months as with cases of APPIS). Testing included quantified proteins C and S, antithrombin, factors VIII/ IX/ XI, fibrinogen, lipoprotein(a), homocysteine, lupus anticoagulant, anticardiolipin antibodies, and genotyping Factor V Leiden (FVL), Factor II G20210A, and MTHFR C677T mutations. 77 Control participants were age and sex matched from healthy patients undergoing elective procedures. Control patient samples were used to identify normal ranges for the laboratory measures and as comparison to values from the prothrombotic group. The primary outcome measure was to determine any association between perinatal stroke diseases and thrombophilia.

No difference was seen in 12 out of the 14 parameters, including all the thrombophilias. Mean INR and PTT were marginally shorter in children with NAIS. The rates of FVL, FII, and MTHFR mutations were similar to controls. Antiphospholipid antibodies were also comparable to controls and resolved on repeat testing. The total number of abnormalities was also comparable between the groups. There were no cases of stroke recurrence. Limitations included failing to test mothers of neonates and not testing some described thrombophilias associated with stroke (ex. ADAMTS13). Thrombophilia testing done at 12 months does not account for possibility of disordered coagulation during the acute time of stroke. Data on family history of thrombosis was not included.

❖ There is no clear association between thrombophilia and idiopathic perinatal stroke. Due to an extremely low risk of stroke recurrence, thrombophilia testing in this population is not indicated.

Sickle Cell Disease

Piel, FB et al, 2017, The New England Journal of Medicine

❖ This is a very nice review article on Sickle Cell Disease focusing on genetic and non-genetic modifiers of the disease.

Section 2. Leukemia and Lymphoma & Bone Marrow Transplantation

Imatinib discontinuation in chronic myeloid leukemia patients with undetectable BCR-ABL transcript level: A systematic review and a meta-analysis

Campiotti, L et al, 2017, European Journal of Cancer

Tyrosine kinase inhibitors (TKIs) have revolutionized the way in which chronic myeloid leukemia (CML) is treated, but it is unclear when - if ever - it is safe to discontinue TKIs and what the risk of relapse is after discontinuation. This study is a systematic review and meta-analysis of the literature evaluating the incidence of CML relapse following the discontinuation of TKIs in adult patients. A literature search was performed using MEDLINE and EMBASE, and two independent reviewers performed the study selection. Studies were considered eligible if they included CML patients who discontinued TKIs, were randomized controlled trials or cohort studies and reported clinical outcomes.

15 cohort studies were included in the final analysis, encompassing 509 patients with CML, all who were treated with imatinib. Overall rate of molecular relapse of CML was 51%, with 80% of relapses occurring within the first six months following TKI discontinuation. All patients were still alive at the two-year follow up and only one patient in the entire cohort progressed to a blast crisis. Most of the trials included had only adult patients and none of the trials were RCTs. Furthermore, the confidence intervals calculated for all sub-analyses overlapped and there were a number of questions that were unable to be answered through the data gathered by this study. All patients included in the study were treated with imatinib, and there was no representation of any of the other TKIs commonly used in clinical practice.

❖ TKIs have proven very effective in the management of CML, but questions remain regarding the duration of therapy required. This study showed that it is feasible to discontinue TKI therapy when in complete molecular remission, given that overall survival after two years was 100%, and that nearly half of patients will not relapse following discontinuation. Further study of the timing of TKI discontinuation is required.

Increased proportion of mature NK cells is associated with successful imatinib discontinuation in chronic myeloid leukemia

Ilander, M et al, 2017, Leukemia

The study analyzed function and phenotype of T and NK cells in relation to successful tyrosine kinase inhibitor cessation in patients with chronic myeloid leukemia. The study was conducted by the Nordic CML study group as a substudy to EURO-SKI clinical trial. 132 adult patients with CML who were treated with imatinib / dasatinib / nilotinib for at least 3 years and sustained deep molecular response for at least 1 year were included. Patients then had monthly RQ-PCR tests to monitor for loss of major molecular response. Blood samples were drawn before stopping TKI, 1 month and 6 months after and analysed by flow cytometry for basic NK, B and T cell counts and proportions. Additional NK and T cell function and immune phenotype were also studied in 45 patients.

Analysis found that having higher proportion of NK cells at time of imatinib discontinuation was associated with increased molecular relapse-free survival (73% vs 51% at 6 months, hazard ratio 2.17, P=0.02). NK cell phenotype in non-relapsing patients have higher proportion of mature NK cells than early relapsing group. The study only included adult patients, and results from patients on imatinib were presented only (due to small number for dasatinib and nilotinib). Findings may not be directly applicable to pediatric patients with CML.

❖ This study contributes to understanding on how the functional state of the immune system relates to whether CML patients can discontinue imatinib treatment.

Mercaptopurine Ingestion Habits, Red Cell Thioguanine Nucleotide Levels, and Relapse Risk in Children With Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group Study AALL03N1.

Landier, W et al, 2017, Journal of Clinical Oncology

Children with ALL are given restrictive guidelines on how to take their oral chemotherapy (6-mercaptopurine) in order to maximize medication bioavailability (in the evening, on empty stomach, without dairy) but which may interfere with chemo adherence. Due to the established link between outcome and adherence to oral chemotherapy, the COG conducted a prospective study (AALL03N1; 441 patients) to look at the association of ingestion habits and adherence, red cell thioguanine levels (TGN) and ultimately relapse.

Adherence was measured using a medication event monitoring system that recorded when medication bottles were opened along with questionnaires and institutional outcome data. After adjusting for other prognostic factors (including adherence), there was no association between ingestion habits and relapse risk or red cell TGN levels. Taking medications at varying times of day was associated with non-adherence (43.8%). This study was limited by its observational design, lack of data on reasons for varying ingestion patterns along with some missing prognostic information like MRD.

❖ Overly restrictive guidelines around oral chemotherapy administration for children with ALL are not necessary and may in fact contribute to lower medication adherence which is known to be prognostic. The COG chemo guidelines as well as our local practice has changed to promote the importance of consistent medication administration above all else.

Childhood Hodgkin International Prognostic Score (CHIPS) Predicts event-free survival in Hodgkin Lymphoma: A Report from the Children's Oncology Group

Schwartz, CL et al, 2017, Pediatric Blood & Cancer

This study aimed to develop a predictive model for event-free survival (EFS) using upfront clinical data in a retrospective cohort of pediatric/adolescent Hodgkin lymphoma (HL) patients. The predictive model was then used for risk stratification. This study was sponsored by COG/NCI. This study included 1103 intermediate-risk HL patients registered on COG AHOD0031 who were randomized between an experimental arm or to standard therapy. Patients randomized to the experimental arms were excluded. Independent predictors of EFS were identified and used to create a prognostic score called the Childhood Hodgkin International Prognostic Score (CHIPS). Half of the patient cohort was used as a training group, and the other half was used to validate the CHIPS.

The following criteria were found to be independent predictors of EFS with similar hazard ratios (1.56-2.7): stage 4 disease, large mediastinal mass, low albumin, and fever. 4-year EFS corresponded to a CHIPS score of 0, 1, 2, and 3, respectively: 93.1%, 88.5%, 77.6%, and 69.2%. The CHIPS was able to identify sub-cohorts with different EFS outcomes (EFS 91.5% with CHIPS 0 or 1, EFS 74.9% for CHIPS 2 or 3). This score was tested in a limited cohort of intermediate-risk patients and therefore might not be extrapolated to low risk or high-risk patients. With evolving and improved therapies for HL, it is difficult to say whether this score will still be valid.

❖ The CHIPS provides an easy and inexpensive predictive model for intermediate-risk patients with Hodgkins Lymphoma but it needs to be validated prospectively and with larger patient numbers.

Donor-to-Recipient ABO Mismatch Does Not Impact Outcomes of Allogeneic Hematopoietic Cell Transplantation Regardless of Graft Source

Damodar, S et al, 2017, Biology of Blood and Marrow Transplantation

There is controversy and conflicting reports regarding the influence of ABO mismatch on outcomes of allogeneic stem cell transplants and how to integrate ABO mismatch in the considerations of donor selection. This large retrospective study from the University of Minnesota assesses the impact of ABO mismatch on outcomes of allogeneic transplants from various graft sources. Transplant outcomes of 1502 patients who underwent SCT from various graft sources between 2000 and 2014 were analyzed.

ABO match status did not significantly influence the outcomes of either engraftment, acute or chronic GVHD or NRM, regardless of stem cell source.

❖ These results suggest that ABO matching should not be a major factor in choosing a donor for allogeneic stem cell transplant.

Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPPescalated alone or in combination with rituximab (HD18): an open-label, international, randomized phase 3 study by the German Hodgkin Study Group

Borchmann, P et al, 2017, The Lancet Oncology

Data suggests the use of interim PET assessment during chemotherapy is superior to baseline international prognostic scoring in terms of predicting long-term treatment outcome in patients with Hodgkin's lymphoma (HL). PET-2 (PET scan after 2 cycles of chemotherapy) has shown a high positive predictive value for patients with advanced HL given ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine). Further, the results of uncontrolled studies suggest there might be a benefit of treatment intensification for patients with advanced HL given ABVD; however, there is no evidence from controlled trials on the prognostic or predictive value of PET-2 for patients given ABVD or BEACOPP.

In this open-label, international, randomized phase 3 trial, patients aged 18-60 years with advanced stage HL were recruited. All patients initially received two courses of BEACOPPescalated. Those patients without progress with PET-positive disease after two courses of BEACOPPescalated (PET2) were randomly assigned (1:1) to receive standard treatment, additional six courses of BEACOPPescalated or six courses of R-BEACOPPescalated.

Consolidating radiotherapy with 30Gy was recommended if a follow up PET showed positive residual disease.

From May 2008-2011, 1100 patients were enrolled, with 440 patients having a positive PET-2 and were randomly assigned to either BEACOPPescalated (220) or R- BEACOPPescalated (220). With a median follow-up of 33 months for PFS, estimated PFS was 91.4% for the BEACOPPescalated group and 93% for those in the R- BEACOPPescalated group ($p=0.99$). The chemotherapy regimen itself might have affected the PET-2 imaging results. In contrast to studies with ABVD, patients in this trial received relevant doses of corticosteroids. Additionally, all patients received G-CSF, which can cause false PET-positive findings in the bone marrow and spleen. However, these G-CSF effects can usually be discriminated from active lymphoma tissue. The time interval of 3-7 days between the last day of treatment and the PET-2 imaging was relatively short. Finally PET after two courses of BEACOPPescalated took place about two weeks earlier than after treatment with ABVD (6 vs. 8 weeks, respectively).

Additionally, the use of consolidating radiotherapy for patients with PET-8 positive residual disease at the end of chemotherapy (34% of PET-2 positive patients) might have contributed to the unexpectedly good PFS and accordingly, poor positive predictive value of PET-2 in this trial. However, with regard to the absence of any positive predictive value of PET in this trial, the most important reason is the likelihood and frequency of progression-free survival events, which affects the power of predictive factors generally. Current randomized studies report failure rate of about 30% for ABVD in patients with stage III and IV disease. Thus, the number of PFS events in patients with advanced stage HL given ABVD is about three times higher than after treatment with BEACOPPescalated followed by radiotherapy to PET-8 positive residual disease in the HD18 study. The analysis does not allow any conclusions on the negative predictive value of PET-2. Although the positive predictive value of PET-2 is poor in this study, a negative PET-2 might still allow the reduction of chemotherapy in PET-2 negative patients.

❖ The addition of rituximab to BEACOPPescalated did not improve the PFS of PET-2 positive patients with advanced stage HL. However, PFS survival for PET-2 positive patients was much better than expected, exceeding even the outcome of PET-2-unselected patients in the previous HD15 trial. Thus, PET-2 cannot identify patients at high risk for treatment failure in the context of the German Hodgkin Study Group standard treatment for advanced stage HL: BEACOPP escalated.

Prognostic significance of flow-cytometry evaluation of minimal residual disease in children with acute myeloid leukaemia treated according to the AIEOP-AML 2002/01 study protocol

Buldini, B et al, 2017, British Journal Of Haematology

In children with acute myeloid leukaemia (AML), assessment of initial treatment response is an essential prognostic factor; methods more sensitive than morphology are still under evaluation. In this study the measurement of minimal residual disease (MRD) was reported by multicolour flow-cytometry (MFC) in one centralized laboratory assessed at the end of each of the 2 courses of induction therapy.

This is a retrospective analysis of 142 children with newly diagnosed AML between May 2003 and May 2011 enrolled in the Associazione Italiana di Emato Oncologia Pediatrica (AIEOP)-AML 2002/01 trial with the aim of evaluating the prognostic role of MFC-MRD. All patients had cytogenetic and molecular characterization at diagnosis and were stratified as either “standard risk” (SR) or “high risk” (HR), according to cytogenetic criteria and response to first induction course. Bone marrow aspirates were collected after the first induction course in 142 patients; 94 of them were also analyzed after the second induction course.

MRD value $\geq 0.1\%$ at the end of the first induction course has a relevant power to predict patient outcome. Children with positive MRD after induction remain at higher risk of relapse and have poorer outcomes as compared to those with a negative MRD. Relapse in children with MRD negative disease appeared to be correlated with high risk genetic features. MFC-MRD cannot detect minor subclones of AML which can be cause of relapse. MFC-MRD has a lower limit of sensitivity of 0.1%.

❖ MRD evaluation can be complemented by presenting features, such as genetic abnormalities or high WBC at diagnosis, with the goals of refining risk stratification and, thus, improving the outcome of children with newly diagnosed AML. This study complements other work done by COG and the BFM showing that end-induction MRD is prognostic in AML.

Monitoring of childhood ALL using BCR-ABL1 genomic breakpoints identifies a subgroup with CML-like biology

Hovorkova, L et al, 2017, Blood

This was a retrospective study that analyzed MRD samples of patients treated for childhood Philadelphia-positive ALL or CML in Australia and the Czech Republic. The study was run by a group that has previously shown discrepancies between Ig/TCR-based and BCR-ABL1 transcript based MRD testing for patients with Philadelphia-positive ALL. This study further details the concordance of the MRD methods and looks at related outcomes. Samples from 48 patients with BCR-ABL1 positive childhood ALL and 3 with CML in blast crisis were analyzed. Each sample had MRD measured by fusion transcript quantification and by clonal Ig/TCR rearrangement. BCR-ABL1 breakpoints were defined by genomic means as opposed to the more standard method of measuring the fusion transcript.

The majority of patients showed good correlation of MRD levels with the different technologies. Genomic (as opposed to transcriptomic) MRD testing also showed differences from Ig/TCR but was consistent with MRD using the BCR-ABL1 fusion-transcript. Only ALL blasts were BCR-ABL1 positive in patients with concordant MRD. However, in patients with discordant MRD, cell sorting showed the presence of non-blast B-, T- and myeloid cells harbouring the BCR-ABL1 fusion. No significant difference in outcome between patients with concordant and discordant MRD were seen.

Patients were treated on several different trials. The study used a small sample size to compare outcomes. They were unable to identify the genomic breakpoint in 20% of patients.

❖ Different MRD tests yield different results - as expected, PCR-based MRD has a higher sensitivity than flow cytometry-based MRD. The presence of multi-lineage BCR-ABL1 positive cells in patients with discordant MRD suggests that a multipotent hematopoietic progenitor cell is affected similar to CML-like disease. Although different MRD methods yield different results, the clinical significance of this is unclear.

Section 3. Oncology: Solid Tumors and Neuro-Oncology

Feasibility, toxicity and response of upfront metaiodobenzylguanidine therapy followed by German Pediatric Oncology Group Neuroblastoma 2004 protocol in newly diagnosed stage 4 neuroblastoma patients

Kraal, K et al, 2017, European Journal of Cancer

The primary aim of this German study was to determine the feasibility and toxicity of upfront MIBG therapy followed by a standard high-risk protocol in high-risk neuroblastoma. This study is a retrospective, multi-centre analysis of a cohort pilot regimen which included all consecutive newly diagnosed stage 4 neuroblastoma patients. The protocol involved two courses of upfront MIBG therapy, followed by the standard high-risk arm of the GPOH NB 2004 protocol (6 courses of induction chemotherapy), followed by surgery. Patients who achieved a response continued on to autologous stem cell transplant followed by radiation to the primary tumor site and retinoic acid. Response rates were assessed post MIBG cycles, post induction chemotherapy and post stem cell transplant.

Upfront MIBG therapy was given to 21 of 32 patients (11/32 were MIBG non-avid). Twenty out of 21 patients received MIBG within two weeks of diagnosis, which was the target for feasibility. Response rate following stem cell transplant was improved for the MIBG group compared to the chemotherapy-only group (71% vs 36%) and was comparable to other MIBG treatment studies. The main limitation to this study is the fact that it is not a randomized trial, and there was selection bias implicit in the different arms, which was compounded by the small numbers included in the trial.

❖ Upfront MIBG therapy in stage 4 neuroblastoma is feasible, the toxicity is acceptable compared to chemotherapy only regimens and it shows a similar response rate to other MIBG treatment trials; however, there continue to be questions around the optimal time point for the incorporation of MIBG therapy into neuroblastoma treatment protocols.

Reduced and Compressed Cisplatin-Based Chemotherapy in Children and Adolescents With Intermediate-Risk Extracranial Malignant Germ Cell Tumors: A Report From the Children's Oncology Group

Shaikh, F et al, 2017, Journal of Clinical Oncology

Children with intermediate risk (IR) germ cell tumors (GCT; Stage II-IV testicular, II-III ovarian and I-II extra-gonadal, stage I with recurrence after surgery alone) have excellent outcomes when treated with 4 cycles of PEb (Cisplatin, Etoposide, Bleomycin every 3 weeks). However, the risk of significant late effects such as hearing loss, neuropathy, nephrotoxicity, second malignancies, and cardiovascular disease has prompted the COG to study the effectiveness of a dose reduction strategy for these patients based on non-inferiority data on a similar regimen in adults with GCT, albeit with weekly Bleomycin.

This was a phase 3, single arm trial (from 2003 to 2011) with a stopping threshold of an EFS of < 92%. 210 patients were enrolled and treated with 3 cycles of PEb with compression from 5 days to 3 days per cycle. EFS was 89% with a 4-year OS of 97% but enrollment was stopped early due to EFS less than the 92% target. However, post hoc analysis revealed that Stage I and II patients treated with 3 cycles had similar outcomes to historical controls treated with 4. The EFS was significantly worse for Stage IV patients when compared to historical counterparts. More grade 3/4 neutropenia was seen on the 3-day regimen. This study was limited by its single arm design, relatively small sample size and patient heterogeneity.

❖ The data from this study do not support a reduction of therapy to 3 compressed cycles for all IR GCTs. However, it is not known whether the use of weekly Bleomycin would compensate for the reduction of cycles as this was not tested. A subset of patients with lower stage tumors may still benefit from a reduction to 3 cycles and this needs further dedicated study.

Landscape of combination immunotherapy and targeted therapy to improve cancer management

Colli, LM et al, 2017, Cancer Research

Targeted drugs aim to inhibit molecular pathways that are crucial for tumour growth and maintenance. Immunotherapy endeavours to stimulate a host immune response. Combining these strategies might be more effective and improve clinical outcomes. Over 13,000 somatic profiles of adult patients were analyzed to identify targetable mutations according to the NCI-MATCH list. Theoretical response to checkpoint inhibitors is based on available exome-wide non-synonymous mutations counts, which can vary by tumor and stage.

In this study, 8.9% of cases from 17 tumor types, displayed profiles that could benefit from combination therapy. Frequently targetable mutations identified were: PIK3CA, BRAF, NF1, NRAS, and PTEN. High burden of NsM (non-synonymous mutations) were found in cases with targetable mutations in SMO, DDR2, FGFR1, PTCH1, FGFR2, and MET. Limitations of the study: the samples are limited by availability from the database. Also, the NSM as clinical relevant predictor to checkpoint inhibitors has not been validated. Whether the combination strategy will be clinically relevant remains unclear.

❖ This study has shown that in adult solid tumors such as melanoma, lung adenocarcinoma and squamous-cell carcinoma, colon, bladder and gastric cancer the combination strategy of targeted therapy and checkpoint inhibitors is theoretically feasible in about 10% of the patients. If this is clinically relevant, remains unclear. Whether results would be applicable to pediatric solid tumors is unknown and further research is needed to predict efficacy of individualized regimens in pediatric cancer patients.

Quality assessment of lymph node sampling in rhabdomyosarcoma: A surveillance, epidemiology, and end results (SEER) program study

Lobeck, I et al, 2017, Journal of Pediatric Surgery

Regional lymph node sampling is an important part of management of paratesticular rhabdomyosarcoma (RMS) in boys over 10 years of age and for staging in extremity RMS. This study aimed to determine the compliance of regional lymph node (LN) sampling in a pediatric population with extremity RMS and paratesticular RMS over the age of 10 years. The retrospective study used SEER registry data for patients in the USA with histologically confirmed RMS who had LN sampling data and age documented (from 2003 to 2008). 537 patients with extremity RMS (aged ≤ 19 years) and 65 pts with paratesticular RMS (10-19 years) were analyzed.

138 of 537 (25.7%) patients with a RMS of the extremities and 31 of 65 (47.7%) had LN sampling done. Lack of LN sampling/excision had a significant impact with decreased patient survival (HR 0.176, $p=0.02$). Mean follow up was 39 months. Data excluded patients with missing LN sampling documentation (54% extremity RMS and 59% paratesticular RMS, so difficult to interpret if this is under-reporting or absence of LN sampling. Unable to interpret why sampling was not carried out. No indication on whether procedures were done in pediatric or adult centres. 17 cancer registries were included, so results may not be generalizable.

❖ Lymph node dissection is standard of care in management of patients with paratesticular RMS and this study indicates that there are discrepancies in adherence to surgical guidelines in RMS which could impact survival. Ongoing awareness and education of LN sampling for surgeons and oncologists is needed but results may not be applicable to all pediatric oncology centres.

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

Long-term neurologic health and psychosocial function of adult survivors of childhood medulloblastoma/PNET: a report from the Childhood Cancer Survivor Study

King, AA et al, 2017, Neuro-Oncology

The authors wanted to investigate the long term neurologic and psychosocial outcomes for adult survivors of pediatric medulloblastoma/PNET who were treated with craniospinal irradiation (CSI) and chemotherapy. This is a retrospective cohort study. The authors used data from the Childhood Cancer Survival Study (CCSS) with patients diagnosed between 1970-1986. They randomly selected a subset of survivors of medulloblastoma/PNET, and identified and recruited siblings closest in age. A self-administered baseline questionnaire was given to survivors and siblings to understand demographics and health-outcomes. Cancer diagnosis and treatment details including chemotherapy protocol and radiation exposure were abstracted from the medical chart using CCSS protocol.

The authors recruited 380 survivors and 4031 sibling pairs to the study. 73% of survivors were 5 years from diagnosis. Forty patients had a stroke, with 25 reported >5 years from diagnosis. Of notes, none of the cumulative incidence curves leveled off at 30 years, indicating patients were still suffering events for decades after diagnosis. 70.6% of patients were alive 30 years from diagnosis. Primary tumor recurrence was 18%. 30-year incidence of 2nd malignant neoplasm was 8% (thyroid cancer, malignant brain tumor, sarcoma). Only 25% of survivors achieved a bachelor's degree.

Retrospective study, it only represents about 30% of patients diagnosed from 1970-1986, so there could be some bias. There is also no separation between those with PNET and medulloblastoma, although they were all treated similarly in this era. This is also not representative of what many patients would be treated with today (reduced CSI dose for SR medulloblastoma of 23.4 Gy, all patients would typically receive chemotherapy), so it may not be generalizable to patients undergoing treatment today.

❖ Survivors of medulloblastoma/PNET are at increased risk for neurologic deficits, lower academic achievement and underemployment as adults. Neurologic events, including hearing loss, seizures, cataract development and stroke continued to occur up to 30 years from diagnosis. Long term follow-up including regular hearing and vision assessment is important in this population.

Late Effects Of Blood And Marrow Transplantation

Imamoto Y, et al, 2017, Haematologica

❖ This is a nice review on late effects in adult patients after hematopoietic stem cell transplantation focusing on detection and interventions.

Second Primary Malignant Neoplasms and Survival in Adolescent and Young Adult Cancer Survivors

Keegan, T et al, 2017, JAMA oncology

It is well known that second primary malignant neoplasms (SPMs) are often associated with prior cancer treatment. Adolescent and young adult (AYA) survivors are considered to have the highest absolute excess risk of SPMs among all age group. However, no study has assessed the survival impact of different SPMs in AYAs compared with pediatric and older patients until now.

Using data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, the authors have compared survival of patients with SPMs with their corresponding first primary cancer types. The secondary outcome was to assess if there were age-specific differences in survival after SPMs. From 13 SEER registries, all patients diagnosed with a primary malignant neoplasm (PM) or SPM during 1992 to 2008 were included. Only 14 common AYA cancers were considered for this study.

A total of 15,954 pediatric, 125,750 AYA and 878,370 older adult patients with a diagnosis of 14 cancers occurring as a PM or SPM were included in the analysis. As expected, the 5-year relative survival for all selected cancers were lower for those with SPMs than those with a PM. Focusing on AYA, with the exception of melanoma and testicular cancer who had a relative high survival for both PM and SPMs, the 5 year relative survival for all other SPMs was lower when compared to the corresponding PMs in AYAs. In multivariable-adjusted models, secondary Hodgkin lymphoma and thyroid cancer had a more than a 3-fold increased risk of death. There are the classical limitations of a study using the SEER registry: risk of unrecorded variables, variations in data coding and reporting, migration of patients in and out of SEER registry areas, lack of detailed treatment information.

❖ Keeping in mind the inherent limitations, this study on a significant number of patients (1,020,074) outlines how SPMs seem to have an inferior relative survival and higher risk of cancer death for AYA and pediatric patients compared with the older population with cancer. This underlines once more the importance of treatment protocols aiming at reduction of treatment toxicity in our pediatric and AYA patients with cancer, whenever this is appropriate and good surveillance protocols for early recognition of SMNs.

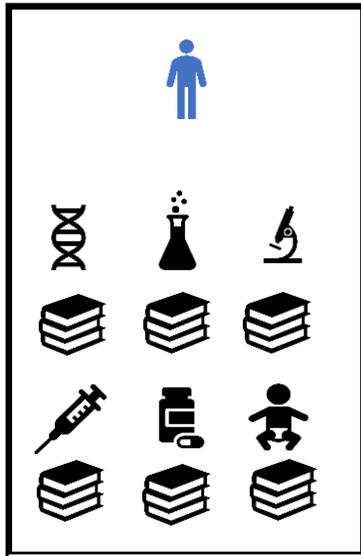
Cancer Risk After Pediatric Solid Organ Transplantation

Yanik EL et al, 2017, Pediatrics

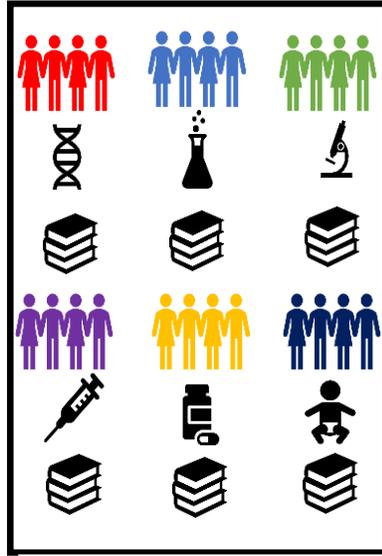
Solid organ transplant (SOT) recipients are known to have a higher risk of cancer, in particular NHL and HL. Previous studies to better understand pediatric PTLD were done in single centre settings. This study linked the scientific registry of transplant recipients (captures all solid organ transplants in US) with 16 US state or regional central cancer registries (described as reliably capturing all cancer diagnosis, except basal cell and squamous cell carcinoma of the skin) to identify pediatric transplant recipients in the US from 1987-2011.

Pediatric solid organ transplant patients had an increased risk of cancer (>19 times higher) compared to general population. Cancers included: NHL (212 times higher), Hodgkin's lymphoma (19 times higher), leukemia (4 times higher), myeloma, cancers of liver, soft tissue, ovary, vulva, testis, bladder, kidney and thyroid. No increased incidence of brain or bone cancers was found. Risk of NHL was highest during first year, in EBV negative recipients, intestine transplant, and induction immunosuppression. Limited by the quality and amount of data entered into the registries (example EBV serostatus missing for 52% of included transplants). Oldest age at follow up was 38 years of age, thus we don't know the risk of cancer later in life for pediatric SOT recipients.

❖ Pediatric Solid organ transplant recipients have a significantly higher risk of cancer (in particular NHL, HL) but also many cancer types including leukemias and solid tumours compared to general population (and adult SOT recipients).

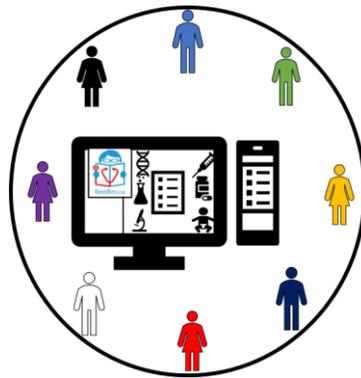


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