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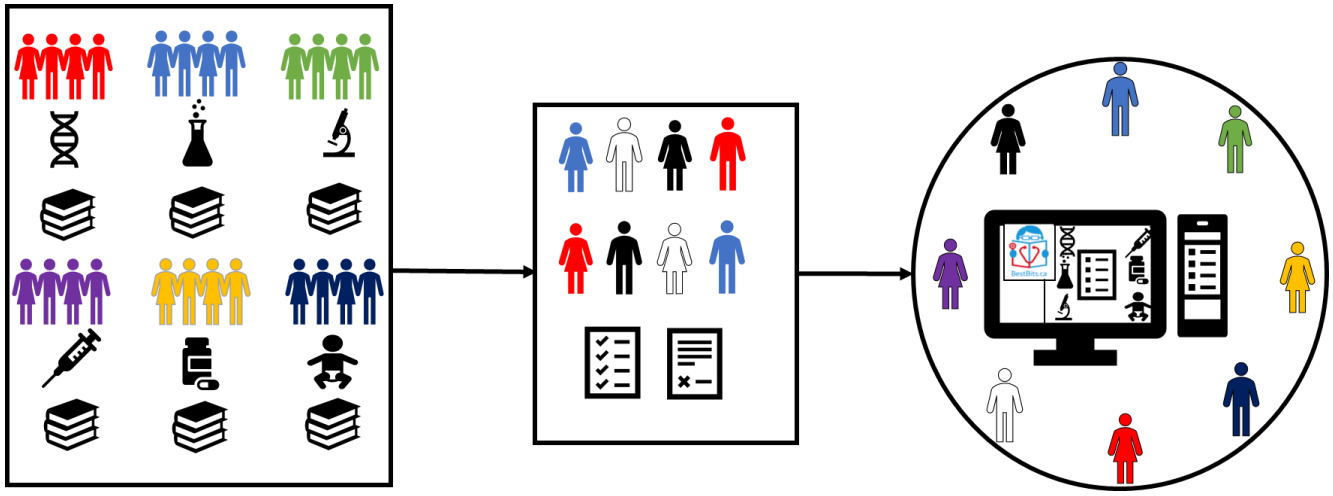
BestBits of the Pediatric Hematology Oncology literature



Introduction

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

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BestBits of the Pediatric Hematology Oncology Literature

Section 1. General Hematology, Thrombosis & Transfusion Medicine

Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII

Reding HJ et al, (2017), Journal of Thrombosis and Haemostasis

This study is a pharmaceutical company sponsored trial with the aim to assess the efficacy and safety of a recombinant factor VIII (FVIII) product with prolonged-half-life for prophylaxis and treatment of bleeds in patients with severe hemophilia A. This is a multinational, phase 2/3, partially randomized, open-label trial. The study included 132 patients with severe haemophilia A, aged 12-65 years. Patients were treated in three individually tailored dose regimens for prophylaxis (according to individual bleeding rate either twice weekly if >1 bleed present in the run-in phase of the study, or randomised to once every 5 days or once every 7 days if no or one bleed occurred in the initial stage). Patients also received the product on demand if there was bleeding. The study period was 10 weeks run-in period followed by 26 weeks of treatment. The study outcome was annualized bleeding rate, response to treatment of bleeds (excellent, good, moderate or poor) and the number of infusions to treat bleeds.

The prolonged half-life of BAY 94-9027 resulted in effective prophylaxis at dose intervals up to every 7 days, given it being tailored to the patient's individual bleeding tendency. It was also effective in treating acute bleeds. No patient developed inhibitors to FVIII during the study. Open-label design and subjective nature of the patient-reported assessment of treatment of bleeds. Study period may not be long enough to detect development of inhibitors.

❖ New factor VIII products with prolonged half-life can offer some hemophilia A patients the convenience of less frequent prophylaxis, which may improve the compliance and quality of life. Their benefits, however, will have to be weighed against their cost.

Evolution Of Disease Activity And Biomarkers On And Off Rapamycin In 28 Patients With Autoimmune Lymphoproliferative Syndrome

Klemann C et al, (2017), Haematologica

This is a Letter to the Editor describing 28 cases of autoimmune lymphoproliferative syndrome (ALPS) treated with rapamycin therapy, addressing first- versus second-line therapy, comprehensive biomarker responses, and the consequences of stopping rapamycin.

❖ Very useful description of a patient cohort treated with rapamycin. Also giving advice on levels of rapamycin that are usually active in this particular cohort.

An international registry of survivors with Hb Bart's hydrops fetalis syndrome

Songdej D et al, (2017), Blood

Hb Barts Hydrops Fetalis was universally fatal until the advent of intrauterine transfusions. As the first cohort of survivors grows up, data about their long-term outcomes can be collected and reported. This is an updated report from a multicentre registry of survivors. 69 patients are in the registry including 39 who have survived past 5 years of age. Intrauterine transfusion resulted in a lower incidence of hydrops (17% vs 55%) but were not associated with differences in long term outcomes. As expected, all patients remained transfusion dependent except for those who underwent HSCT. 64% of patients had at least one congenital anomaly - limb defects being the most common. 31% of survivors had severe height and weight undergrowth. 11/33 survivors older than 5 who had neurodevelopmental testing had moderate to severe delay. Registry data - no control over interventions.

❖ Survivors with Hb Barts may have significant developmental issues as they grow older. Hematologists managing these patients should be aware of this complication in order to include it in counselling and to be able to implement early referral.

Section 2. Leukemia and Lymphoma & Bone Marrow Transplantation

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Davids MS et al, (2017), Journal of Clinical Oncology

This is a phase I adult study of a new inhibitor of BCL-2, an anti-apoptotic protein, called venetoclax. It is of relevance to paediatrics because this target is also thought to be important in paediatric leukaemia/lymphoma and potentially neuroblastoma.

Phase I dose escalation study in patients with non-Hodgkin lymphoma (part of a larger study that also included patients with CLL). Standard phase I inclusion criteria and toxicity grading according to CTCAE.

Maximum tolerated dose was not defined (no dose level exceeded 30% DLT rate). Manageable side effects. Impressive evidence of clinical benefit in context of phase I. Interesting that despite this being a phase I study with max 6 dose levels, 106 patients were enrolled. Reflects a growing trend for significant expansion within the context of a phase I to demonstrate efficacy once dose has been determined.

❖ BCL-2 inhibitor, venetoclax is a potentially interesting drug for paediatric leukemia/lymphoma and neuroblastoma in the future. A paediatric phase I study will be opening shortly.

Risk–Benefit Analysis of Pediatric-Inspired Versus Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone Protocols for Acute Lymphoblastic Leukemia in Adolescents and Young Adults

Guzauskas GF et al, (2017), Journal of Adolescent and Young Adult Oncology

This study aimed to estimate the risk–benefit trade-off of a pediatric-inspired regimen compared with hyper-CVAD for first-line treatment of AYA patients with Philadelphia-negative ALL. A quantitative evaluation of the risks and benefits of pediatric versus hyper-CVAD therapy in AYA ALL patients may provide useful guidance for patient-specific treatment decisions and development of treatment guidelines.
This was a retrospective analysis of two studies already published and comparison between the two. This exploratory analysis seems to be the first comparative quantitative assessment of the potential benefits and harms associated with a pediatric-inspired protocol versus a hyper-CVAD protocol for the treatment of Philadelphia-negative AYA ALL

This analysis used a 6-state Markov model to evaluate the risks and benefits of using a pediatric-inspired protocol compared with hyper-CVAD. Patients could transition among the health states at intervals of 1 month, with a total time horizon of 10 years. Patients modeled for the hyper-CVAD protocol were from a single-center, long-term, follow-up study of hyper-CVAD in 288 patients, of whom 17% were Philadelphia chromosome–positive. For the pediatric protocol, comparable patient data were used from a retrospective study of 85 patients treated with a pediatric-inspired regimen (modified Dana Farber Cancer Institute pediatric protocol (DFCI 91-01)). The primary outcomes were total life-years and total quality-adjusted life-years for each regimen.

Treatment with the pediatric-inspired protocol was associated with a 0.04 increase in life-years, but a 0.01 decrease in QALYs at 1 year. By years 5 and 10, the pediatric-inspired protocol resulted in 0.18 and 0.24 increase in life-years and 0.25 and 0.32 increase in QALYs, respectively, relative to hyper-CVAD. The lower quality of life associated with the induction and intensification phases of pediatric treatment was offset by more favorable progression-free survival and overall survival relative to hyper-CVAD.

The authors chose these two studies after systematic literature review because they assessed that they were the most comparable in regard to patient characteristics. However, patients' characteristics were not the same in all respects. Also,

they had to make assumptions regarding outcomes in Philadelphia-negative patients, since the hyper-CVAD source included Ph-positive patients. Finally, they didn't compare pediatric-inspired protocol to augmented hyper-CVAD. So the conclusion of the study can bias in favor of pediatric-inspired study.

❖ In the absence of randomized controlled trials comparing these two types of protocols, this retrospective analysis suggests that, compared with hyper-CVAD, pediatric-inspired protocols may increase life-years throughout treatment stages and QALYs in the long term. However, it does not compare pediatric-inspired to augmented hyper-CVAD. It seems to support the use of "more intense" regimens for AYA in order to achieve better outcomes even if there is a higher risk of complications during treatment.

Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase 1 trial

Wang CM et al, (2017), Clinical Cancer Research

Hodgkin lymphoma (HL) is typically CD30 positive. The authors were looking for a novel treatment for relapsed or refractory disease. CD30 targeting CAR-T cells have not been described prior to this report. This is a phase 1 study describing the feasibility, safety and efficacy of CD30 targeting CAR-T cells.

18 patients with relapsed or refractory HL between the ages of 13-77 years with CD30+ disease (17 HD, 1 ALCL). Patients received one of three conditioning regiments (fludarabine/cyclophosphamide, gemcitabine/cyclophosphamide or paclitaxel/cyclophosphamide) with subsequent infusion of CAR-T cells given over several days. They were eligible for a second infusion of CAR-T cells at recurrence if they had an initial response.

Of 18 patients enrolled, 14 had refractory disease, 4 had relapsed disease that was refractory to prior treatment. There were 2 grade 3/4 toxicities - one patient with elevated ALT, and one with decreased left ventricular systolic function. One patient had anaphylaxis. Out of the 18 patients, there were 7 partial responses and 6 with stable disease. Five patients were previously treated with brentuximab, 1 had PR and 2 had SD after CAR-T cells. Lymph node regions responded the best, lung lesions responded poorly.

Varying conditioning regimens were used prior to infusion. Study included patients who have failed previous CD30 targeted therapy (ie brentuximab), but there were some patients with response. These cells are specifically engineered for the patient, and this is difficult to make available widely.

❖ CD30 targeted CAR-T cells are safe to give and show some efficacy in relapsed/refractory CD30+ve Hodgkin lymphoma in this phase 1 study. Additional studies are needed to further characterise their role in therapy for Hodgkin lymphoma.

Clinical impact of minimal residual disease in children with different subtypes of acute lymphoblastic leukemia treated with Response-Adapted therapy

Pui CH et al, (2017), Leukemia

This study aimed to determine the relevance of MRD assessment at two points during induction therapy. The authours postulated that an early MRD at day 19 could identify a subgroup of very good prognosis leukemia. This clinical trial was part of the St Jude Total Therapy XV study.

Bone marrow MRD was assessed on days 19 and 46 of induction therapy by flow cytometry, PCR, or both. MRD-based risk classification had 3 levels based on the two time points and not corrected for method of MRD measurement. A total of 488 children were included in the study. The mean EFS and OS for global population were respectively 85.8% and 92.5%. MRD level was significantly associated with both EFS, OS and CRR for the global population. Patients with either t(12;21)

or hyperdiploid ALL and negative day 19-MRD had particularly good prognosis. A day 19-MRD level >1% was associated with a high mortality rate for the subgroup of T-ALL and NCI standard-risk B-ALL with a respective OS of 68.5% and 76.7%. Day 46-MRD level positivity was predictive of poorer OS and higher risk of relapse for both NCI standard and high-risk B-ALL.

This is a well conducted study with large accrual and long term follow-up allowing the evaluation of 10-year EFS and OS. Philadelphia positive ALL (Ph-ALL) were not included because of the low number (10). The fact that the study did not mandate the method of measuring MRD may have introduced bias

❖ This study confirmed the relevance of MRD assessment in ALL and the clinical impact of measuring MRD twice in induction. Other groups including COG and AIEOP measure MRD at two time points as well albeit with different chemotherapy backbones. The new very low risk groups identified here may be candidates for therapy reduction. A similar study is already underway in COG (AALL0931).

Treatment of relapse after allogeneic stem cell transplantation in children and adolescents with ALL: the Frankfurt experience

Willasch AM, (2017), Bone Marrow Transplantation

Relapse after allogeneic stem cell transplantation in ALL patients is very challenging to treat and there is no standardized treatment approach. In this study, the latest experience from the Frankfurt group is presented, describing a curative second transplant and an experimental non-transplant approach for treatment of post transplant relapse.

In this single center retrospective study, outcomes of all relapsed pediatric ALL patients treated in Frankfurt between 2005 and 2014 were analysed. The treatment strategy was to treat all patients who were in good clinical condition with high dose chemotherapy or specific immune-therapy to induce remission followed by a second transplant from a haploidentical donor conditioned with clofarabine, cyclophosphamide, etoposide, alemtuzumab and fludarabine. If a second transplant was not clinically feasible, a combination of low dose chemotherapy and donor lymphocyte infusions was offered.

A total of 23 out of 101 pediatric ALL patients relapsed after their first SCT during the study period. Seven patients were treated with a second transplant after responding to salvage chemo/immune therapy, out of which five remained in CR. Ten patients who where not clinically feasible for a second transplant were treated with low dose chemotherapy and DLI out of which four remained in CR. Four-year overall survival for the transplant approach was 56% and for the experimental non-transplant approach 40%.

This is a retrospective single center study with a very limited number of patients and no control group. Treatment group was directed largely by physician decision thereby introducing bias.

❖ The two presented approaches to treat post-transplant relapse in ALL show encouraging results. Larger prospective studies are warranted.

Phase 1 study of anti-CD22 antibody-drug conjugate pinatuzumab vedotin with/without rituximab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma

Advani RH et al, (2017), Clinical Cancer Research

This is a phase 1 study using pinatuzumab (anti-CD22 monoclonal antibody conjugated to a microtubule disrupting agent) in relapsed/refractory mature B cell lymphomas and CLL. The aim was to determine the phase 2 dose and evaluate the safety, tolerability, pharmacokinetics and preliminary antitumor activity of pinatuzumab.

This was a phase 1 study with a 3+3 dose escalation design of relapsed/refractory patients with: DLBCL, follicular lymphoma, marginal zone lymphoma or small lymphocytic lymphoma, mantle cell lymphoma or CLL. They did NOT have

to have CD22 expressed on tumor cells to be eligible. All patients were >18 years. Initial cohort was enrolled to determine maximum tolerated dose (MTD). An expansion cohort with DLBCL or iNHL was enrolled to determine preliminary efficacy at MTD. An additional cohort was enrolled to determine safety and efficacy of pinatuzumab combined with rituximab. Pinatuzumab was given every 21 days.

91 patients were enrolled, 75 receieved pinatuzumab alone, 16 received pinatuzumab combined with rituximab. Three patients had grade 4 neutropenia at 3.2 mg/kg, one with delayed recovery. Antitumor activity was only seen at doses >= 1.8 mg/kg. The dose selected for phase 2 trials was 2.4 mg/kg every 21 days. Twenty-five percent of patients with DLBCL responded to pinatuzumab (2 CRs and 3 PRs) with PFS of 4 months. There was 1 PR in DLBCL in the group treated with pinatuzumab and rituximab.

This study was done in adult patients (median age was in the 60's) and they did not require demonstration of CD22 expression on tumor cells before enrollment. This makes interpretation of the efficacy results difficult, although one would presume that the majority of the DLBCL patients had CD22 expression. This information is useful to be aware of for relapsed DLBCL (or other mature B cell lymphomas expressing CD22), but may not be directly translatable to the pediatric population.

❖ Pinatuzumab (anti-CD22 conjugated to MMAE) can be given safely and shows some efficacy in patients with DLBCL in the adult population. This could be a potential choice for pediatric patients with mature B cell lymphomas in the future and should be further explored.

The combination of bortezomib with chemotherapy to treat relapsed/refractory acute lymphoblastic leukaemia of childhood

Bertaina A et al, (2017), British Journal of Haematology

Previous Phase I and II studies have shown that bortezomib, a proteasome inhibitor, has acceptable toxicities and a therapeutic effect in patients with relapsed ALL. This study describes the results of a single centre study which looked at the rate of CR in patients with relapsed/refractory ALL who received a combination of bortezomib and standard salvage chemotherapies.

37 pediatric patients (30 with relapsed/refractory B ALL and 7 with relapsed/refractory T ALL), were enrolled in the study. Bortezomib was administered four times in the first month of treatment, in combination with a standard salvage therapy, including dexamethasone, doxorubicin, vincristine, PEG-asparaginase and IT methotrexate. Response to treatment was assessed morphology, cytogenetics and immunophenotyping on day 29.

Twenty-two of 30 B-ALL patients (73%) and five of seven T-ALL patients (71%) achieved CR with the addition of bortezomib to their chemotherapy regimen. Fourteen of the 37 patients had a negative MRD at the end of therapy resulting in a higher 2-year OS of 68.4%. The MRD positive group had dismal survival. The main limitations of this study include the small sample size, involvement of a single centre and lack of head to head comparison via a randomized control trial.

❖ Bortezomib has been shown to be safe in combination with standard salvage chemotherapy. Where cytotoxic agents such as bortezomib fit in the treatment of relapsed/refractory ALL in the age of immunotherapy is not clear.

Genomic characterization of paediatric acute lymphoblastic leukemia: an opportunity for precision medicine therapeutics

Tasian et al, (2017), British Journal of Haematology

This is an excellent review of the genomics of pediatric acute lymphoblastic leukemia (ALL) by Dr. Tasian and Dr. Hunger.

Increased regulatory T cell graft content is associated with improved outcome in haematopoietic stem cell transplantation: a systematic review

Fisher SA et al, (2017), British Journal of Haematology

GVHD is a major cause of morbidity and mortality in patients post hematopoietic stem cell transplant (HSCT). Previous studies have indicated that low amounts of regulatory T cells in the grafts were found in patients who developed GVHD. This article is a systematic review of studies which reported the regulatory T cell (Treg) composition of donated grafts to determine if the amount of Tregs in a graft influence clinical outcomes, specifically in regards to GVHD incidence and severity.

A systematic review was done using defined eligibility criteria, and involved both adult and paediatric data. The search was limited to articles published in 2000 and onward. Five reviewers were involved in determining eligible studies. Forty-eight references were identified, describing 14 independent studies and 987 participants.

Consistent reports were found throughout the identified studies. Significant improvement was found in overall survival associated with high Tregs in most studies, as well as significant reduction in acute GVHD incidence; however, no studies showed an effect of Treg number or ratios on the incidence of chronic GVHD. Only 2 studies were included in a meta-analysis for overall survival but high Tregs were associated with increased survival ($p = 0.003$).

The included studies were conducted at different centres with heterogeneous indications for transplant, recipient demographics and co-morbidities, sources of allografts, conditioning, Treg measurement method, and post-transplant management. Many of the studies included were small and likely under-powered, and there may be a risk of small study and publication bias.

❖ This systematic review indicates a clear and consistent benefit to higher levels of regulatory T cells in allogeneic haematopoietic stem cell transplants. Improvement of Treg/T cell ratios for HSCT allografts could prove to be an effective measuring in decreasing the risk of acute GVHD. Further multi-centre, prospective trials with standardized methods of measuring Tregs are warranted.

The Genetics and Molecular Biology of T-ALL

Girardi T et al, (2017), Blood

❖ A good review of the different molecular alterations found in T-ALL with a focus on possible druggable alterations.

Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab

Abaza Y et al, (2017), Blood

In the past couple of decades, acute promyelocytic leukemia (APML) treatment has been revolutionized by the successful use of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) to the exclusion of cytotoxic chemotherapy. As this regimen is relatively novel, long-term outcomes have not yet been reported.

This is a follow up of 187 patients (age 10 and above) from 3 consecutive MD Anderson trials using ATRA, ATO, and one dose gemtuzumab-ozogamicin to high-risk patients and low risk patients with leucocytosis during induction. A priori primary outcomes were event-free survival (EFS), disease-free survival (DFS), and overall survival (OS). These trials were not randomized. At 5 years, EFS, DFS, and OS were 87%, 99%, and 89% respectively for the low risk group and 81%,

89%, and 86% for the high risk group. Survival was lower for patients > 60 years of age. This is a single centre trial and non-randomized.

❖ These long term outcomes lend further support for ATRA and ATO as standard of care for APML.

In utero cytomegalovirus infection and development of childhood acute lymphoblastic leukemia

Francis SS, et al, (2017), Blood

Maternal infections during pregnancy are suspected to play a role in the development of childhood ALL through generation of genomic instability. So far, scientific evidence for this theory is controversial. This article addresses the question whether maternal viral infections are associated with ALL. The retrospective case-control study was done as part of the California Childhood Leukemia Study (CCLS).

The study was set up in a two-step approach by (1) screening of the diagnostic bone marrow of 127 ALL and 38 AML patients for presence of viral particles by using a comprehensive next-generation sequencing (NGS)-based viral and bacterial metagenomics assay; and then after identification of candidates: (2) targeted viral DNA sequencing by digital droplet PCR of the candidate pathogens in newborn dried blood spot DNA of 268 ALL cases and 270 healthy controls.

Neonatal cytomegalovirus (CMV) was identified as a candidate in the first part of the study as it was significantly more prevalent in the bone marrow of patients with ALL compared to AML (OR 18, p=0.03). In the second phase, CMV was detected in neonatal dry blood spots of cases and controls and was associated with an increased risk of ALL (OR 3.71, CI 1.56-7.92). In a subgroup analysis, this association was only significant in Hispanics and not in non-Hispanic whites.

This study used two highly sensitive assays (NGS) to detect CMV particles in the bone marrow of ALL and AML patients and by another highly sensitive assay after birth in ALL cases versus healthy controls. The significance of using these techniques clinically for viral detection is unclear. Interesting, the association was not found in a subgroup analysis of non-Hispanic whites which raises questions on the generalizability of the results.

❖ The study contributes to the theory that infections could contribute to the development of ALL with the finding that CMV was more prevalent in dried blood spots after birth of ALL cases.

Section 3. Oncology: Solid Tumors and Neuro-Oncology

A comparison of safety and efficacy of cytotoxic versus molecularly targeted drugs in pediatric phase I solid tumor oncology trials

Dorris K et al, (2017), Pediatric Blood and Cancer

Until now there was no direct comparison of toxicity and efficacy data between cytotoxic and targeted agents in paediatric oncology clinical trials. This systematic review collected safety and response data for classes of anticancer agents based on a review of past clinical trial results to help guide future phase I/II clinical trial designs for novel targeted drugs.

Systematic review of pediatric phase I recurrent/refractory solid tumor trials. Published reports were evaluated for patient characteristics, toxicity information, and response rates. 143 phase I paediatric solid tumor clinical trials were identified, enrolling 3,896 children. 61 trials investigated 53 targeted drugs and 82 trials evaluated 48 cytotoxic agents.

Cytotoxic drugs had a higher objective response rate but also higher dose limiting toxicities and hematologic toxicities. There was no difference between cytotoxic and targeted agents in non-hematologic toxicities and progression free survival. The biggest limitation is that meta-analyses of small underpowered trials are likely to result in false positives and negatives. This was a high degree of heterogeneity amongst the included articles. For example, there was no universally accepted method of reporting toxicities.

❖ Keeping in mind the inherent limitations, cytotoxic agents were found to have a significantly higher response rate and toxicity profile compared to targeted agents. Hematologic toxicity profiles of targeted agents are generally more tolerable and may be more favourable for relapsed patients.

Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group.

Janssens G et al, (2017), European Journal of Cancer

Overall survival of patients with diffuse intrinsic pontine glioma (DIPG) is poor. Current treatment approach consists of upfront irradiation followed by best supportive care. With this strategy, a transient reduction in symptoms can be achieved in most patients but subsequent deterioration and death usually occur within one year. Survival time benefits were shown in smaller pilot studies using re-irradiation at secondary deterioration with acceptable toxicity. The purpose of this study was to analyze benefit and toxicity of re-irradiation at first progression of diffuse intrinsic pontine glioma (DIPG).

This is a multicenter retrospective matched-cohort analysis of children aged 2-16 years with characteristic features of DIPG or biopsy-proven high-grade glioma after first progression. An interval of ≥3 months after upfront radiotherapy was required before re-irradiation. Thirty-one children with DIPG, underwent re-irradiation (dose 19.8–30.0 Gy) alone (N=16) or combined with systemic therapy (N=15). Thirty-nine patients fulfilling the same criteria receiving radiotherapy at diagnosis formed the matched comparative cohort. They were followed by best supportive care (n = 20) or systemic therapy (n = 19) but without re-irradiation at progression. Thirty-nine patients without re-irradiation received best supportive care or systemic therapy only.

Significant benefit in median OS (13.7 versus 10.3 months; P = .04) was observed in favor of patients undergoing re-irradiation. Clinical improvement with re-irradiation was observed in 24/31 (77%) patients. Re-irradiation was well tolerated with no recorded grade 4–5 toxicities. Re-irradiation itself and the interval between upfront radiotherapy and re-irradiation remained independent prognostic factors for OS. A risk score using five categories was useful to predict time of survival at first progression.

This is a retrospective study, and reasons for choosing re-irradiation or another treatment are not revealed. Surprisingly, progression-free survival was not affected by radiotherapy at progression which raises questions about the main outcome of the study.

❖ Re-irradiation was associated with prolonged overall survival in this retrospective analysis with median OS of 3.4 months for patients with DIPG undergoing re-irradiation at the first progression without major toxicity. More importantly, symptom improvement was observed in nearly 80% of the patients. The study and SIOP-E recommendations, suggest re-irradiation of children with DIPG at the first progression can be considered.

Prevention of radiotherapy-induced neurocognitive dysfunction in survivors of paediatric brain tumours: the potential role of modern imaging and radiotherapy techniques.

Ajithkumar T et al, (2017), Lancet Oncology

Neurocognitive dysfunction is the leading cause of reduced quality of life in long-term survivors of pediatric brain tumours with radiotherapy being a main contributor to this. This is a review of the potential role of modern imaging and innovative radiotherapy techniques with the goal of minimizing neurocognitive sequelae in children with brain tumours and how to integrate such strategies into further research. Such techniques include evaluation of photon radiotherapy such as image-guided radiotherapy, volumetric nodulated arc therapy, helical tomotherapy and adapative radiotherapy along with proton beam radiation and heavy in therapy.

This article is a descriptive summary of various advanced techniques in radiotherapy to limit long term sequelae as well as proposing strategies to integrate such advances in further research. The only technique thus far that has achieved some success to limit long-term sequelae is avoidance of radiation particularly in those less than 3 years of age, and reduction of the total radiation dose and brain volume irradiated.

❖ Minimizing neurocognitive sequalae in children with brain tumors is challenging. Avoidance of radiation especially in under 3 years and reduction of radiation dose and brain volume irradiated, are the most successful strategies to date.

Comprehensive Molecular Characterization of Pheochromocytoma and Paraganglioma

Fishbein et al, (2017), Cancer Cell

As part of the Cancer Genome Atlas project, this study aimed to provide a comprehensive genomic characterization of Pheochromocytomas (PCC) and Paragangliomas (PGL) (n=173). Molecular profiling was undertaken using 6 different tools: whole-exome sequencing (for mutations), SNP array (copy number variations), mRNA sequencing (gene expression, aberrant fusions), microRNA sequencing, DNA methylation and reverse-phase protein arrays.

Overall, these rare endocrine tumors have a low incidence of genomic alterations. In addition to the 2 subgroups already described in previous transcription studies - "pseudohypoxia" (including alterations in genes involved in regulation of hypoxia transcription factors VHL, EPAS, SDH, FH, MDH2, and IDH1) and "kinase signaling" (RET, HRAS, NF1), the group describes 2 additional transcriptional groups: The "Wnt-altered" cluster of tumors is characterized by WNT pathway activation; novel MAML3 fusion gene and CSDE1 somatic mutation correlate with poor clinical outcome. This group of tumors expressed the highest levels of chromogranin A (CHGA, a clinical marker of neuroendocrine tumors that correlates with metastatic disease). The forth cluster of "cortical admixture" tumors: despite higher content of normal tissue/leukocyte infiltration these had specific genetic alterations, such as MAX mutations, suggesting that they are a separate entity. 27% of the tumors were associated with a known germline mutation and exome sequencing did not reveal any novel germline mutations.

❖ PCC/PGL comprise 4 different subgroups with specific genetic drivers. Amongst the many genetic drivers identified, specific mutations - both germline and somatic - were mutually exclusive.

Implications for clinical practice are the confirmation/identification of molecular markers of aggressive disease (SDHB, mutations ATRX and MAML3 fusions) and a rationale to explore targeted therapies (such as HIF in "pseudohypoxia" tumors and WNT proteins in "WNT signalling" tumors.

Posterior fossa syndrome: Review of the behavioral and emotional aspects in pediatric cancer patients

Lanier JC et al, (2017), Cancer

About 25% of children after posterior fossa tumor resection develop posterior fossa syndrome consisting of varying degrees of mutism, ataxia/hypotonia, and emotional lability. This review outlines the current knowledge of this entity including therapeutic approaches.

❖ Posterior fossa syndrome is a very challenging entity for patients, their families, and clinicians alike and this review is a good summary.

Needle tract seeding after percutaneous biopsy of sarcoma: Risk/benefit considerations

Berger-Richardson D et al, (2017), Cancer

Needle tract seeding after percutaneous biopsy of sarcomas is a common fear but is based on case reports or series mainly. This review summarizes current data on needle tract seeding after percutaneous biopsy.

❖ Needle tract seeding after percutaneous biopsy of sarcomas with recurrence of the tumor was very low in available data (below 1%) despite significantly higher prevalence of malignant cells in excised needle tracts (4 to 22%).

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

Eliciting the child's voice in adverse event reporting in oncology trials: Cognitive interview findings from the Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events initiative

Reeve BB et al, (2017), Pediatric Blood and Cancer

The main goal of this qualitative cognitive interview study was to establish, evaluate, and refine the PRO-CTCAE (Patient-Reported Outcomes version of the NCI's CTCAE) measures to be comprehensible to children and their caregivers, and relevant for capturing AEs, in order to improve care and precision of AE grading in trials. The study aimed to refine the measures and stratify the children into different age groups.

Children/adolescents ages 7-20 receiving treatment for cancer from 7 pediatric research hospitals and their parent-proxies were included. Pediatric PRO-CTCAE includes 130 questions that assess 62 symptomatic AEs, in child-friendly terms. First round of interviews elicited concepts and terminology from participants and was used to refine the Paediatric PRO-CTCAE questions tested in the second round to obtain specific feedback. Interviews were stratified by age group.

45 children and 42 proxies participated. Some words/stems that were found to be challenging in the first round of interviews were changed in the second round and were well understood. 7-8-year-olds had difficulty with the 7-day reference period for symptoms. Most questions in the Paediatric and Proxy PRO-CTCAE were well understood by participants and proxies. Patients who had experienced a particular AE were better able to accurately report it. Small sample sizes for each item (although consistent with recommended guidelines). Participants likely did not represent the sickest patients. As well, some children did not feel well which may have affected their full attention during the interviews.

❖ Development of patient reported outcome tools in pediatrics are important to improve the way adverse events are reported and graded on clinical trials. The Paediatric and Proxy PRO-CTCAE performed well, particularly among older children, who were able to read, understand, and report symptoms. The next step is to validate the tool in a longitudinal multisite study to detect changes in symptom status over time and compare self-report AEs with relevant clinical anchors.

Pregnancy outcome following hematopoietic cell transplantation for thalassemia major

Santarone S et al, (2017), Bone Marrow Transplantation

Hematopoietic stem cell transplantation (HSCT) offers a definitive cure for patients with β–thalassemia major at the expense of permanent infertility as a consequence of this treatment modality. This study follows the course and outcomes of pregnancies of β-thalassemia female patients and partners of male patients who were successfully treated with allogeneic HSCT.

The methods of conception and delivery, course and outcomes of 42 post-transplant pregnancies occurring in 15 female patients and partners of 8 male patients with β–thalassemia major who were successfully treated with allogeneic HSCT in a single center from Italy were investigated. All patients received myeloablative conditioning with busulfan and cyclophosphamide (200 mg/kg), and treated with cyclosporine and methotrexate for GVHD prophylaxis.

In the female patients, 9 of the 15 patients (60%) needed post-transplant hormonal supplementation to restore normal menses. Twenty-one pregnancies (78%) were achieved with spontaneous conception in 11 women. Six pregnancies were achieved in 4 women following either in vitro fertilization and embryo transfer or heterologous ovo-donation. There were two cases of miscarriage, a high rate of complications (59%) and a remarkably high (22.7%) rate of preterm delivery. Delivery by Cesarean section was observed in 18 of the 22 pregnancies (82%). The partners of the male transplanted

patients had uncomplicated pregnancies. Conception was spontaneous and natural in all cases and was followed by uncomplicated outcome with normal gestational age at birth and no miscarriage. This study describes a small fortunate group of patients who successfully achieved pregnancy post HSCT but the actual fertility of this patient group cannot be estimated as the proportion of patients trying to get pregnant is unknown.

❖ Some β–thalassemia major patients post allogeneic HSCT retain or recover their fertility after transplant at the expense of an excess in complications and preterm delivery.

Graft-versus-host disease targets ovary and causes female infertility in mice

Shimoji S et al, (2017), Blood

Female survivors of allogeneic HSCT have a high incidence of ovarian dysfunction. While this has been assumed to be an effect of conditioning, the role of GVHD on ovarian function has not been explored. Mouse models of GVHD were established with three different conditioning regimens - BuCy myeloablative, BuCy RIC, and TBI followed by splenocyte transplant. One cohort received prophylaxis with prednisolone, cyclosporine, or tacrolimus while a control cohort had no prophylaxis. Fertility and ovarian function were assessed by histology, measurement of granulosa cell secretions, and by mating studies.

Mice with GVHD had lower levels of ovarian function and low levels of fertility by mating studies regardless of conditioning regimen. Fertility, however, was preserved in animals who received GVHD prophylaxis. Outcomes were not dependent on the conditioning regimen. This is a mouse study and may not necessarily translate to humans. The mice in this study also only received conditioning and did not receive the chemotherapy that precedes HSCT in humans with malignancies.

❖ Whether GVHD affects fertility and ovarian function in women is an important question raised by this paper and needs to be further studied.

Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consort

Skinner, R et al, (2017), Lancet Oncology

The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was developed to critically examine the evidence and harmonize existing long-term follow-up guidelines. The European Union-funded PanCareSurFup (PCSF) Consortium collaborated with IGHG to identify treatments associated with increased risk of impaired spermatogenesis, testosterone deficiency, and physical sexual dysfunction in male childhood, adolescent and young adult (CAYA) cancer survivors, and evaluate surveillance strategies. The aim of the recommendations is to enhance evidence-based care for male CAYA cancer survivors. This is a collection of systematic reviews. The senior author Dr. Dan Green is well known for cancer survivorship at St. Jude's.

Guideline representatives from the North American Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), Scottish Intercollegiate Guidelines Network (SIGN), United Kingdom Children's Cancer and Leukaemia Group (CCLG), PCSF Consortium, and other international paediatric oncology societies developed a working group of experts from nine countries.

The experts looked for areas of concordance and discordance across the COG, DCOG, SIGN, and CCLG guidelines. They devised clinical questions to address areas of discordance for surveillance of impaired spermatogenesis, testosterone deficiency, and physical limitations that lead to sexual dysfunction (subsequently described as physical sexual dysfunction) covering the following key issues: who needs surveillance; which surveillance modality should be used; how often and for how long surveillance should be performed; and when survivors should be referred. The authors performed systematic searches in the medical literature for studies of CAYA survivors.

❖ These are very extensive international harmonized guidelines for surveillance of male CAYA survivors and will be helpful resource for counselling and managing patients in long-term follow-up.

Family Strategies to Support Siblings of Pediatric Hematopoietic Stem Cell Transplant Patients

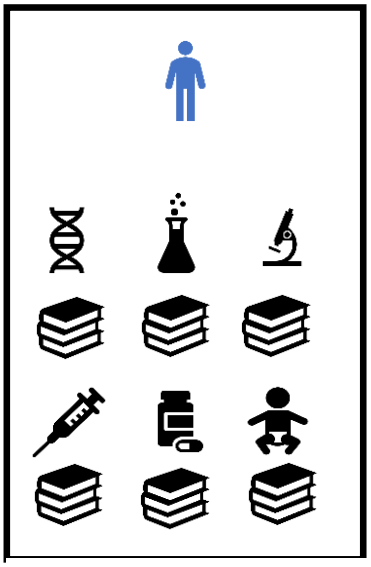
White TE et al, (2017), Pediatrics

A systemic analysis (Gerhardt et al., PBC, 2015) concluded that siblings of children with cancer are at risk for long-term issues (including psychosocial distress, poor functioning) and should receive supportive services. This study intended to describe the strategies families have used to address the needs and concerns of siblings of children undergoing HSCT.

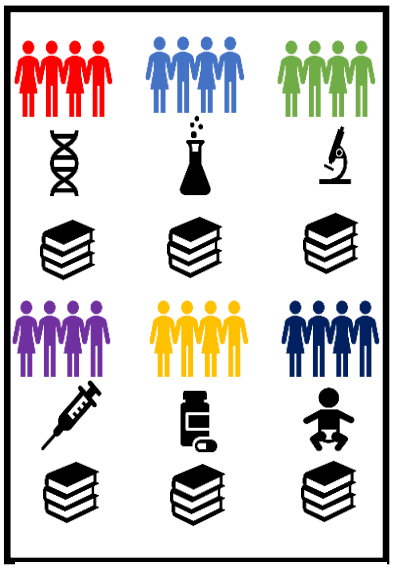
This was a qualitative study in three parts: (1) analysis of interviews of 26 families at 4 sites in US/Canada within a year hematopoetic stem cell transplantation (2) 6 families were interviewed to focus on sibling issues and strategies used to support siblings from 1 site (Children's Healthcare of Atlanta) (3) 15 health care professionals were interviewed regarding strategies they use to reduce stress in siblings.

Strategies identified included: sharing information (emphasized by children more than adults), using social support (family and friends to help), taking siblings to the hospital, communicating virtually, providing special events or quality time for siblings, offering siblings a defined role to help the family, switching between parents at the hospital, keeping the sibling's life as constant as possible and arranging sibling meetings with a child life specialist or counselor. The parent study's primary aim was different and grounded theory was used thus not all families were asked the same questions around siblings and limited numbers may not be applicable to all families.

❖ We know it is important to support families (including siblings) during the stress of treatment. This study will help us provide concrete examples of strategies other families have used to support siblings.



Keeping up with the literature can be challenging on your own …



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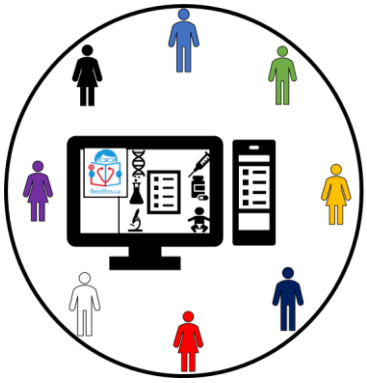

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