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Issue 2

Journal Club: The Lightning Rounds

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Introduction

Journal Club: The Lightning Rounds 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 hematologist and oncologists.

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Journal Club – The Lightning Rounds

Section 1. General Hematology, Thrombosis & Transfusion Medicine

A multicenter randomized controlled trial of intravenous magnesium for sickle cell pain crisis in children.

Brousseau D (2015) Blood (Link to Abstract)

Multicentre, randomized, parallel, double blind, placebo-controlled trial comparing: intravenous Magnesium 40 mg/Kg q8 hourly versus normal saline plus standard therapy for the treatment of pain crisis for patients with Sickle cell anemia. Hypothesis it would reduce length of stay (LoS), opioid use and improve QoL.

204 children eligible: n=101 magnesium and n=103 placebo. The addition of intravenous magnesium did not shorten length of stay, reduce opioid use, or improve quality of life in children hospitalized for sickle cell pain crisis.

◈ IV Magnesium doesn't help children with SCD pain crisis.

Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomized, multicenter, placebo-controlled trial.

Grainger JD (2015), Lancet (Link to Abstract)

Eltrombopag is a thrombopoietin receptor agonist, which is used effectively in adults with chronic immune thrombocytopenia. This study involved a randomized, multicenter, placebo-controlled, double blinded study looking at the safety and efficacy of eltrombopag in pediatric patients with chronic ITP. 92 patients: 63 in the treatment arm and 29 in the placebo arm. 40% of patients achieved platelet counts of greater than or equal to 50 during the initial 12 weeks of the study, while only 3% of the placebo treated group achieved these counts. 80% of patients achieved a platelet count of greater than 50 in the 24 weeks following the randomized portion of the study, when all patients were treated with Eltrombopag. There was no significant difference in adverse events between the two groups.

◈ Eltrombopag, a thrombopoietin receptor agonist, is a suitable therapeutic option to consider in pediatric patients with chronic ITP.

Comparison Of Long-Term Outcomes Between Children With Aplastic Anemia And Refractory Cytopenia Of Childhood Who Received Immunosuppressive Therapy With Antithymocyte Globulin And Cyclosporine.

Hama A (2015) Haematologica (Link to Abstract)

The 2008 World Health Organization classification proposed a new entity in childhood myelodysplastic syndrome, refractory cytopenia of childhood (RCC). However, it is unclear whether this morphological classification reflects clinical outcomes. This study is a review on the outcome among 186 children who had received immunosuppressive therapy (IST, horse ATG / cyclosporine) for acquired aplastic anemia. Patients were divided into 3 groups after re-classification by bone marrow pathology: aplastic anemia (AA), refractory cytopenia of childhood (RCC), refractory cytopenia with multilineage dysplasia (RCMD). The AA group had significantly lower leukocyte/neutrophil/reticulocyte/platelet counts compared to the RCC and RCMD groups. No difference in response rates to IST among the 3 groups was seen. Cumulative incidence of total clonal evolution showed no significant difference among the groups. However incidence of development of monosomy 7 was higher in the AA group. Longer duration of G-CSF administration was associated with development of monosomy 7 in AA patients. 10-year failure-free survival did not differ significantly among the 3 groups. 10-year overall survival was significantly lower in the AA group (85%) vs the RCC group (97%) and the RCMD group (100%).

◈ The 3 groups did not appear to be distinctly different in terms of biology and outcome in this study. Clonal evolution is still seen in the AA group. This hints that the current morphological classification may not be reliable enough to distinguish aplastic anemia from hypocellular MDS.

Efficacy of transfusion with granulocytes from G-CSF/dexamethasone–treated donors in neutropenic patients with infection.

Price TH (2015), Blood (Link to abstract)

Granulocyte transfusion therapy has been used for 20 years without demonstrating clear efficacy in treating infections in neutropenic patients. This report from a multicenter randomized controlled trial included patients with neutropenia and proven/probable/presumed infection. Subjects were randomized to receive either standard antimicrobial therapy (n=56) or standard antimicrobial therapy plus daily granulocyte transfusions from donors stimulated with granulocyte colony-stimulating factor (G-CSF) and dexamethasone (n=58). The primary end point was a composite of survival plus response to antimicrobials, at 42 days after randomization. Transfused subjects received a median of 5 transfusions. Overall success rates were 42% and 43% for the granulocyte and control groups, respectively (P > .99), and 49% and 41%, respectively, for subjects who received their assigned treatments (P = .64). Success rates for granulocyte and control arms did not differ within any infection

◈ There is no evidence for superiority of giving granulocyte transfusions in addition to standard care with antimicrobials in subjects with neutropenia and infection.

Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women.

Moretti, D (2015), Blood (Link to Abstract)

54 non-anemic young women (aged 12-49y) with plasma ferritin ≤20 μg/L were recruited and subsets of 13-25 individuals were given labeled iron ($FeSO_4$) at different single doses orally on 1 or on 2 consecutive days, or three 60-mg Fe doses (twice-daily dosing) within 24 hours.

In the single dose administration, 24 hours after doses ≥60 mg, serum hepcidin was increased and the fraction of the iron being absorbed was decreased by 35% to 45%. With increasing dose, fractional absorption decreased whereas absolute absorption increased. Total iron absorbed from 3 doses (2 mornings and an afternoon) was not significantly greater than that from 2 morning doses. Providing lower dosages (40-80 mg Fe) and avoiding twice-daily dosing maximized fractional absorption. The duration of the hepcidin response supported alternate day supplementation.

◈Current dosing recommendations giving iron multiple times a day seem to reduce the iron absorption of subsequent doses by increasing hepcidin with negative feedback on iron absorption from the guts.

Section 2. Leukemia and Lymphoma & Bone Marrow Transplantation

The genomic landscape of juvenile myelomonocytic leukemia.

Stieglitz, E, 2015, Nature Genetics (Link to abstract)

Previous studies have characterized JMML as "Rasopathy", mostly driven by activation of the Ras-MAPK pathway through mutations in NF1, NRAS, KRAS, PTPN11 or CBL. Seeking to understand the mutational landscape of JMML and identify additional pathways involved in disease initiation and progression, the authors performed whole-exome sequencing in serial samples from patients at diagnosis, relapse and transformation to AML.

In addition to known genetic hits, the group identified 2 new mutations in the Ras-MAPK pathway (SH2B3 and RRAS2), as well as activation of JAK-STAT signaling and epigenetic modification through the PRC2 and spliceosome complexes as important in leukemogenesis in JMML. In 16/22 patients that were analyzed over time, the mutations identified at diagnosis were invariably maintained at relapse. Several mutated genes, previously unknown to be implicated in JMML, were identified at relapse (JAK3 and RUNX1).

Contrary to previous reports, they found no difference in outcome between patients harboring different somatic mutations; when corrected for other variables, the number - rather than the type - of mutations at diagnosis was the main determinant of outcome.

◈ JMML is more than a Rasopathy and the discovery of additional molecular alterations provides rationale for new therapeutic approaches (such as demethylating agents) and better patient stratification.

Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia.

Karol SE (2015) Blood (Link to abstract)

The authors performed a genome-wide association study of single nucleotide polymorphisms (SNPs) in a discovery cohort with 2285 children with ALL, treated on the Children's Oncology Group AALL0232 protocol. They found a SNP near the glutamate receptor GRIN3A locus (9q31.1) associated with higher risk of corticosteroid-induced osteonecrosis (hazard ratio = 2.03). In 2 different other cohorts this association was confirmed. The control cohorts included 361 children with ALL on St. Jude's Total XV protocol and 309 non-ALL patients from Vanderbilt University's BioVU repository treated with glucocorticoids. Multivariant analysis revealed age >10 y, and female gender to be associated with higher risk of osteonecrosis. In a meta-analysis osteonecrosis-associated glutamate receptor variants were also associated with other vascular phenotypes including cerebral ischemia and arterial embolism and thrombosis.

◈ This article provides insight into genetic predisposition in glucocorticoid-associated osteonecrosis.

Incidence of breast cancer among female survivors of Hodgkin lymphoma: a US-population–based trend analysis from 1973 to 2011.

Giri S (2015) Blood (Link to abstract)

The NCI database of cancer patient follow up SEER 9 was used to analyze a total of 5776 women with Hodgkin lymphoma followed up for a median duration of 229 months. The authors found an excess risk of breast cancer with diagnosis at a median age of 46 years and a latency of 231 months since HL diagnosis. In contrast the median age for a breast cancer diagnosis in the general population is 61 years (data from the same database). The age-adjusted incidence ratios steadily declined over the study time. The authors speculate that this might be due to advances in radiation techniques (involved field vs extended field), less radiation, differences in chemotherapies or combinations.

◈ This report confirms the excess risk of breast cancer in HL survivors and highlights that these women develop breast cancer at an earlier age. The good news is that the age-adjusted incidence declines.

Targeting casein kinase II restores Ikaros tumor suppressor activity and demonstrates therapeutic efficacy in high-risk leukemia.

Song, C, 2015, Blood (Link to abstract)

Inactivating tumour suppressor Ikaros mutations are associated in humans with high-risk B-cell leukemia resistant to treatment. The authors assessed Ikaros function on cell cycle regulation in various in vitro and in vivo assays (the latter on mouse xenograft models) and showed that decreased Ikaros activity due to the deletion or inactivating mutation of a single IKZF1 allele results in repression of genes regulation cell cycle promotion. Ikaros function was impaired by the pro-oncogenic casein kinase II (CK2), and CK2 is overexpressed in leukemia. CK2 inhibition restored Ikaros function as transcriptional repressor of cell cycle, resulting in an antileukemia effect. CK2 inhibition on mouse xenografts led to decrease in leukemic burden

◈ Restoration of Ikaros tumor suppressor activity via inhibition of CK2 might be a new target in high-risk leukemia with deletion of one IKZF1 allele.

Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT.

Dufour C (2015), British Journal of Haematology (Link to abstract)

The current first-line treatment for patients with SAA without a matched sibling donor is immune suppressive therapy. This study shows very good results with upfront unrelated donor hematopoietic stem cell transplantation (HSCT) for these patients. In a cohort of 29 patients, the 2 year overall survival was 96% and event free survival was 92%, These outcomes were similar to the matched historical sibling donor control group and superior to the matched historical immune suppressive therapy control group.

◈ In a very small cohort using a different conditioning regimen than used in most centres, HSCT unrelated donors appeared to have similar outcomes to historical sibling-related donors.

Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma.

Chen R (2015), Biology of Blood and Marrow Transplantation (Link to abstract)

Brentuximab vendolin (BV, anti CD30 antibody conjugated to monomethyl auristatin E) is currently used in Hodgkin Lymphoma (HL) patients as a third-line treatment usually to bridge to autologous hematopoietic stem cell transplantation (HSCT). In this multicenter prospective phase II trial the activity and toxicity of BV were examined for relapsed/ refractory HL as a second-line treatment, bridging for autologous HSCT. Of 37 patients, the overall response rate was 68%, and the drug was well tolerated, with 32 (86%) of the patients proceeding to autologous HSCT.

◈ This study demonstrated that brentuximab vedotin as second-line therapy for patients with HL is active, well tolerated, and does not hinder stem cell collection or engraftment.

Stem cell transplantation in severe congenital neutropenia: an analysis from the European Society for Blood and Marrow Transplantation.

Fioredda, F. Blood. 2015 (Link to abstract)

This multicenter, retrospective study included patients from the EBMT and SCETIDE registries. 136 Severe Congenital Neutropenia (SCN) patients underwent HSCT between 1990-2012 at European and Middle Eastern centers. Indications leading to transplant included: HD-GCSF requirements (79%), severe infection (37%), transformation to MDS before HSCT (16%).

The following complications were seen: Graft failure: Probability after 90 days from HSCT was 10%, probability of engraftment was 92% in HLA-matched, and 72% in mismatched donor. GVHD: Cumulative incidence at 90 days (grade 2-4) was 21%. 2 factors associated with a significant lower rate of GVHD: HLA-matched related donor and double prophylaxis with CSA and MTX. Peripheral blood as sources of HSCT was associated with higher cGvHD incidence.

Overall Survival: 3-year OS after HSCT 82%. Median time from transplant to death: 3 months, with 80% of the deaths occurring within 12 months after transplant. Transplants undertaken in later years had better survival (OS-3ys 66% in 1990-2000, 79% 2001-2007 and 91% in 2008-2012). No secondary malignancies were reported.

◈ HSCT is an option for treatment of SCN with an acceptable 3 year OS and EFS (82% and 71%, respectively). TRM is 17% and therefore appropriate selection of patients and SC sources as well as GVHD prophylaxis are important factors.

Pediatric T-cell lymphoblastic leukemia evolves into relapse by clonal selection, acquisition of mutations and promoter hypomethylation

Kunz JB, Oct 2015, Haematologica (Link to abstract)

This study aimed to understand the genetic basis for relapse in T-cell ALL. Matched samples of T-cell ALL patients at diagnosis, remission and relapse where analyzed by various deep sequencing methods and DNA methylation array. The investigators found 2 mutation patterns at relapse. Type 1 was derived from major leukemic clones at diagnosis, with additional mutations. Type 2 arose from a common pre-leukemic ancestor, with the relapse clone having new mutations not similar to the major diagnostic clone. Overall there is significant increase in mutational load at relapse compared to first diagnosis. NT5C2 was identified as a recurrently mutated gene and may confer resistance to therapy. Relapse specific genetic changes tend to activate general mechanisms of carcinogenesis rather than known leukemia specific drivers.

◈ This paper implies that there are at least two evolutionary pathways through which T-ALL can relapse.

Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey

Zeiser R, 2015, Leukemia (Link to abstract)

Ruxolitinib is a JAK 1 /2 inhibitor for treating myelofibrosis, which was also reported to be effective for treatment of GVHD in mouse models. This study is a retrospective survey of the outcomes of patients who received ruxolitinib as salvage therapy for corticosteroid refractory GVHD. Data was collected from 19 centers in Europe and the USA. A total of 95 patients were included for analysis (acute GVHD n=54, chronic GVHD n=41). Overall response rate was 81.5% and 85.4%, for aGVHD and for cGVHD, respectively. 6 month survival rates were 79% and 97.4%for aGVHD and cGVHD, respectively. Adverse events observed included increased risk of CMV reactivation, and cytopenias.

◈ Ruxolitinib appears to be a promising new agent for steroid resistant acute and chronic GVHD in a retrospective review.

Diagnostic and prognostic value of 18F-DOPA PET and 1H-MR spectroscopy in pediatric supratentorial infiltrative gliomas: a comparative study

Morana, G (2015), Neuro-Oncology (Link to abstract)

Retrospective review of pediatric patients with supratentorial gliomas or non-neoplastic lesions suspected to be gliomas based on initial MRI. Pts had MRI spectroscopy (MRS) and 18F-DOPA PET within 2 weeks. (Spectroscopy estimates levels of different metabolites, DOPA chosen as uptake of amino acid analogs less in normal brain and uniform in tumor whether enhancing component or not). Twenty-seven patients enrolled aged 4-17 years, 21 with gliomas and 6 with non-neoplastic lesions. Median follow up was 19 months. For PET, sensitivity was 78% (5 false negatives), specificity 83% (1 false positive), accuracy 78%. For MRS, sensitivity was 95% (1 false negative), specificity 83% (1 false positive), accuracy 93%. False negatives for PET and MRS were LGG, and false positive were encephalitis. Statistically significant difference in uptake of DOPA found between HGG and LGG, also seen with choline peaks on MRS, but the difference was lower with MRS. DOPA uptake was also found to be an independent predictor of survival on multivariate analysis. Authors concluded that MRS was better for distinguishing glioma from non-neoplastic lesions as it is more widely available, cheaper and does not involve radiation. DOPA-PET was best for distinguishing low-grade from high-grade lesion.

◈ In the future, non-invasive imaging techniques such as PET and MR spectroscopy may be able to predict pathology and prognosis of brain tumors, specifically gliomas. Biopsy may still be required though, as molecular information to inform potential targeted therapy is becoming more important.

Review: Renal Medullary Carcinoma and Sickle Cell Trait: A Systematic Review

Alvarez, O. Pediatr Blood Cancer 2015 (Link to abstract)

This is a review of RMC which occurs almost exclusively in people with sickle cell trait or sickle cell disease. Whilst the majority of the time hematuria does not represent RMC in these patients, they should be counselled that this is a symptom that warrants further investigation. Mortality may be as high as 95%.

High Prevalence of Hereditary Cancer Syndromes in Adolescents and Young Adults with Colorectal Cancer

Mark M, 2015, Journal of Clinical Oncology (Link to abstract)

This retrospective cohort study from MD Anderson evaluated 193 patients with colorectal cancer who underwent genetic counselling over a 5 year period. They identified 35 % of these patients to have an identifiable hereditary cancer syndrome. Whilst patients with a cancer syndrome were more likely to present at earlier stages and have a family history of cancer, 19 % of the hereditary syndromes were found in individuals with no family history.

◈ Refer ALL adolescents with colorectal cancer for genetic counselling regardless of family history or phenotype!

Cardiovascular mortality after chemotherapy or surgery for testicular nonseminoma: A population based study

Fung C, 2015, Journal of Clinical Oncology (Link to abstract)

This European population-based study quantifies the CVD mortality amongst 15,006 men with testicular non-seminoma over a 30 year period (1980-2010) when cisplatin-based chemotherapy became widely adopted. The authors report a significantly increased CVD mortality after chemotherapy (Standardized Mortality Ratio 1.36) but not surgery. In particular they note a significant excess of deaths in the first year after diagnosis (SMR 5.31) and included cerebrovascular disease (SMR 3.45) and heart disease (SMR 3.45), with distant disease and older age being identified as risk factors.

◈ Think about possibility of CVD in our TYA population with metastatic testicular GCTs even early post chemotherapy, particularly those with identifiable risk factors. Remember VTE prophylaxis.

Germ cell cancer and multiple relapses: toxicity and survival.

Lauritsen J, 2015, Journal of Clinical Oncology (Link to abstract)

This paper looks at the toxicities experienced by the small number of adult patients with extracranial GCTs who receive more than one line of treatment for disseminated disease as well as their overall survival. It is a retrospective cohort study of 268 patients from Denmark. The comparator group were patients with GCT who were treated with only one line of therapy or with surgery only.

The authors report that approximately half of patients requiring more than one line of therapy die of their disease and that for the survivors there is significant increased risk of second cancer, major cardiovascular disease, renal impairment, neurological disorders and death as a result of other causes at median follow up of only 10.8 years.

◈ There is a high risk of subsequent relapse, secondary malignancy, and other late effects in patients treated for refractory GCT. These results could also apply to our adolescent population.

Targeting Human Cancer by a Glycosaminoglycan Binding Malaria Protein

Salanti A, 2015, Cancer Cell (Link to abstract)

Malaria forces erythrocytes to express a protein that binds to a proteoglycan found specifically on placenta which helps to avoid clearance in the spleen. This group found that most carcinomas and sarcomas have this same placental proteoglycan on their surface but that it is rarely found in other normal tissue. The group engineered a recombinant version of the malarial protein and it effectively targeted malignant cells with this surface marker. They then fused this protein to diphtheria toxin and found significant tumor killing effect in a variety of tumors. They have now developed a drug based on this concept called VDC886 that they have tested in mice.

◈This is a totally new approach to targeting more than one cancer type. There is now a new promising drug that is yet to enter the trial pipeline. We now also know about a surface marker specific to malignancy that can be stained for diagnostic purposes.

Dual Targeting of the Autophagic Regulatory Circuitry in Gliomas with Repurposed Drugs Elicits Cell-Lethal Autophagy and Therapeutic Benefit.

Shchors K, 2015, Cancer Cell (Link to Abstract)

This publication outlines multiple related and progressive experiments. Firstly, the authors found that tricyclic antidepressants (TCA) can reduce the progression of low grade gliomas to GBM in a mouse model but does not change the progression or survival in mice who present with GBM. Then, an in-vitro assay measuring proteins generally degraded by autophagy found that TCAs promote autophagy in glioma cells. A high-throughput screen was then done to find a complementary drug that could accentuate the regulatory effect of TCAs on autophagy. Ticlopidine – an anti-platelet agent – had the best activity in this screen through its inhibition of $P2Y_{12}$ which upregulates cAMP and promotes autophagy. They finally tested the combination of these drugs in various in-vitro and in-vivo model finding positive effects on autophagy and increased tumor killing and animal survival.

◈Since GBM is so notoriously difficult to treat, inventive studies are needed. Approaches such as this one that target relatively uninvestigated biological pathways using drugs with already-established safety profiles that are off-patent is a promising way to get new effective treatments to clinic quickly.

Secreted Frizzled-Related Protein 3 (SFRP3) is Required for Tumorigenesis of PAX3-FOX01-Positive Alveolar Rhabdomyosarcoma

Kephart (2015) Clin Can Research (Link to abstract)

In this study, negative regulators of the Wnt pathway were found to be upregulated in an expression array of myoblasts expressing the PAX3-FOXO1 fusion transcript. In particular, a gene called SFRP3 was upregulated and appears to play a key role. In several functional tests this protein was confirmed to be important both for proliferation of alveolar rhabdomyosarcoma (aRMS) cells and for downregulation of the Wnt pathway within those cells. An aRMS xenograft with a suppressible SFRP3 overexpression was established in mice. 5/7 of these mice showed no detectable tumor at necropsy when SFRP3 was suppressed and treatment with vincristine was also given.

◈This study establishes the Wnt pathway and upreguation of SFRP3 in particular as a potential key process in translocation positive aRMS. This may open the door for a targeted treatment in this difficult disease.

Different outcomes for relapsed versus refractory neuroblastoma after therapy with 131I-metaiodobenzylguanidine (131I-MIBG)

Zhou MJ, Eur J Cancer (2015) (Link to Abstract)

Retrospective cohort analysis of 218 patients with refractory or relapsed neuroblastoma treated with 131I-MIBG at UCSF, San Francisco between 1996 and 2014. No significant difference in overall response rates to 131I-MIBG between patients with relapsed versus refractory neuroblastoma was seen. However, in terms of site, residual soft tissue disease a significantly have better response to 131 I-MIBG on univariate analysis compared to other sites like bone and bone marrow.

Patients with prior relapse had higher rates of progressive disease and had lower 2-year overall survival after 131I-MIBG compared to patients with refractory disease. Results showed that with 131I-MIBG, 24% of relapsed patients had progressive disease compared to only 9% of refractory patients, and 39% of relapsed patients had stable disease compared to 59% of refractory patients ($p = 0.02$). The 24-month OS for refractory patients was significantly higher with 65.3% compared to 38.7% for relapsed patients ($p < 0.001$).

◈No firm conclusion can be drawn, however early start of MIBG therapy in refractory cases especially with soft tissue residual disease had better short term survival rates compared to relapsed cases in this cohort.

Inhibition of MEK confers hypersensitivity to X-radiation in the context of BRAF mutation in a model of childhood astrocytoma

Studebaker, A. Pediatric Blood and Cancer (2015) (Link to abstract)

This study explores the use of a MEK inhibitor in combination with ionizing radiation (XRT) in a model of BRAF- mutant anaplastic astrocytoma. The effect of MEK inhibition (selumetinib), XRT or the combination of both was evaluated in subcutaneous BRAF mutant xenografts. Inhibition of MEK signaling in BRAF mutant cells or in xenografts lead to complete suppression of FANCD2 and conferred hypersensitivity to XRT in BRAF mutant xenografts without increasing local skin toxicity.

◈In the context of mutant BRAF in recurrent gliomas of childhood or anaplastic astrocytoma there is a possibility of potentiating XRT effects selectively in tumour cells by using MEK inhibition. This may allow reduced dosing of XRT and consequently reduced late effects.

Poly-ADP-Ribose Polymerase as a Therapeutic Target in Pediatric Diffuse Intrinsic Pontine Glioma and Pediatric High-Grade Astrocytoma

Chornenkyy, Y (2015) Molecular Cancer Therapeutics (Link to Abstract)

This is a preclinical study (from HSC) looking at PARP (poly-ADP-ribose polymerase) expression and inhibition in DIPG and pHGA. Using cell culture, tissue microarray, immunohistochemistry and Western Blotting, they found that PARP1 protein is expressed in pHGA and DIPG patient samples and cell lines - 85% of pHGAs and 76% of DIPG tissue microarray samples expressed PARP. Also they found that Niraparib (an oral PARP inhibitor that has been tested in adult cancer phase 3 trials) is more effective at reducing tumor cell growth than veliparib or olaparib using cell viability kits and colony forming assays. Niraparib was also shown to cause DNA damage and reduce cell proliferation. Pretreatment with this prior to 2 Gy ionizing radiation decreased DNA damage repair and relative cell count. In mice xenografts, Niraparib inhibited PARP1 activity and extended the survival of mice pre-treated with Niraparib before IR by 60% (40 vs 25 days).

◈PARP is demonstrated to be a therapeutic target in DIPG and pHGA. This study is preclinical rationale for Niraparib, an oral PARP inhibitor, to be further investigated as a radiosensitizer prior to radiation in patients with DIPG and pediatric high-grade astrocytoma.

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

Complications of Central Venous Access Devices: A Systematic Review

Ullman AJ (2015), Pediatrics (Link to abstract)

This study is a systematic review looking at the proportion and rate of central venous access device (CVAD) failure and complications in pediatrics across CVAD types. It was found that 25% of all CVADs fail or have significant complications (i.e. become a source of infection or be obstructed from clots). PICCs had a high rate of failure and complications, approximately equal to umbilical catheters in neonates, while, as expected, totally implanted devices were found to have the lowest rates. Many of the causes of the failures were found to be preventable, as quality improvement initiatives in various studies did show improvement in the CVAD survival and function. This study advocates for the careful use of CVADs, which aren't without their risks, and continued quality improvement initiatives to decrease the rates of failure and complications.

◈ Central venous access devices, including PICCs and ports, have significant rates of failure and complications, many of which are due to preventable factors.

Risk of Subsequent Neoplasms During the Fifth and Sixth Decades of Life in the Childhood Cancer Study Cohort

Turcotte L (2015), Journal of Clinical Oncology (Link to abstract)

This is a paper from the Childhood Cancer Survivorship Study, which is a retrospective cohort with ongoing longitudinal observation. This report focuses on 14,364 survivors diagnosed between 1970 and 1986 who were 40 years or older at last contact. It reports the cumulative incidence of new subsequent neoplasms occurring after the age of 40 as 34.6 % with survivors being twice as likely as the general population to receive a diagnosis of subsequent malignant neoplasm after this age. Survivors were at particular risk for breast, renal, thyroid and soft tissue sarcomas. Female sex and therapeutic radiation were identified as risk factors.

◈ Make sure our survivors are aware that their increased risk of second cancer is truly lifelong. Think strategically about screening options.

Prescription Opioids in Adolescence and Future Opioid Misuse

Miech R (2015), Pediatrics (Link to abstract)

This is a prospective study investigating the impact of medically prescribed opioids on the risk that adolescents and young adults will misuse opioids in the future. The study found that there was a threefold increase in the rate of misuse in the group of participants who were judged to be at lowest initial risk of opioid misuse (as designated by previous experiences with illegal substances and attitudes toward drug use), and a 33% increase in risk of misuse overall. Interestingly, no independent increase in the risk was identified in the groups stratified to be at higher risk of opioid misuse initially. Recommendations from this study include using non-opioid pain control measures prior to opioids in an effort to minimize their use, and to carefully counsel adolescents who receive opioids around the risks of opioid misuse and abuse.

◈ Contrary to common teaching, there is actually an increased risk of future opioid misuse in young adults who are appropriately prescribed opioids prior to the end of high school.

Genome-Wide Identification and Characterization of Novel Factors Conferring Resistance to Topoisomerase II Poisons in Cancer

Wijdeven R, 2015, Cancer Research (Link to abstract)

The authors created a panel of knockout haploid cells using CRISPR and tested them systematically to identify gene products related to resistance to topoisomerase II inhibitors. They confirmed that ABCB1 confers resistance and identified 4 new genes that when knocked out lead to resistance to topoisomerase II inhibitors: C9orf82, SMARCB1, SMARCE1, and Keap1. All of these genes are related to repair of double stranded DNA breaks. For the most part, these deletions do not make cells resistant to topo I inhibitors.

◈Given the major toxicities of doxorubicin and etoposide it would be useful to select patients whose tumors will be resistant to these agents. This panel identifies the genes that could help us make thischoice. We will now have to investigate these in animal and human studies.

Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis

Hole J (2015) The Lancet (Link to abstract)

This study is a systematic review of RCTs looking at the use of music in the intraoperative and postoperative period to reduce post-operative pain. The authors ended up with 72 studies that had a control group (white noise, headphones, regular noise, and some others) with varying degrees of quality. Overall the use of music decreased pain, decreased analgesia use, and decreased anxiety regardless of the procedure, whether GA was used or not and whether or not the patient was allowed to choose the music. Limitations include heterogeneity of the quality of included studies and possible publication bias based on the funnel plot.

◈ Likely we can think of music as another form of distraction. We know that distraction is important in controlling children's' pain and perhaps this is another form of distraction that we can use. It hasn't been as well evaluated in children but given the minimal risk profile there is no reason not to use music for patients who request it.

Section 5. Relevant Publications from SickKids staff/fellows (not included above)

Dose level response rates of mTOR inhibition in tuberous sclerosis complex (TSC) related subependymal giant cell astrocytoma (SEGA)

Weidman, D. (2015) Pediatric Blood and Cancer (Link to abstract)

◈ Therapeutic dose of mTOR inhibitor is effective in shrinking TSC related SEGAs. Doses less than 2.5 mg/m2 were insufficient to maintain response in this limited series.

Thalassaemia in children: from quality of care to quality of life

Amid A (2015) Archives of disease in childhood (Link to abstract)

Review article of pathophysiology and advances in clinical care and quality of life in patients with thalassaemia with a focus on developing countries and their resources.