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Issue 1

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

Red blood cell transfusion is associated with increased hemolysis and an acute phase response in a subset of critically ill children.

L'Acqua C (2015) American Journal of Hematology

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/26183122

In this prospective study of critically ill children, the effect of RBC storage duration on extent of hemolysis was examined by comparing laboratory measurements obtained before, and 4 hours after RBC transfusions in 100 patients. They identified a subset of 21 patients with considerable extra-vascular hemolysis accompanied by an acute phase response. Storage duration of the RBC did not correlate with hemolysis and inflammation indicators, suggesting that other recipient and donor factors are more important in the induction of post transfusion hemolysis.

Effects of eltrombopag on platelet count and platelet activation in Wiskott-Aldrich syndrome/X-linked thrombocytopenia

Gerrits AJ, 2015 Blood

Link to abstract: http://www.bloodjournal.org/content/126/11/1367

Platelet activation measured by flow cytometry in 9 Wiskott-Aldrich Syndrome/ X-linked Thrombocytopenia (WAS/XLT) patients and 8 age-matched healthy controls, showed that reduced platelet activation found in WAS/ XLT was directly due to microthrombocytopenia. GP IIb-IIIa and P-selectin were less expressed due to smaller platelet size. Eltrombopag treatment resulted in an increased platelet count in 5 out of 8 patients with WAS/ XLT and 6/8 had reduced clinical bleeding severity. Although the eltrombopag-induced increase in platelet production in WAS/XLT is less than in ITP (sample cohort compared to 7 age-matched ITP patients), it has beneficial effects on platelet counts but not platelet activation in the majority of WAS/XLT patients.

Hydroxyurea treatment does not increase blood viscosity and improves red blood cell rheology in sickle cell anemia.

Lemonne N (2015) Hematologica

Link to abstract: http://www.haematologica.org/content/100/10/e383

Study on 24 adult patients in Guadeloupe with Sickle Cell Anemia: 50% had 1 α-gene deletion, who were given hydroxyurea treatment including escalating doses for history of frequent VOC and or ACS or frequent subclinical VOC and anemia in the preceding year. Outcomes measures: hematocrit (Hct), blood viscosity, red cell deformability and RBC disaggregation threshold as well as clinical VOC and ACS. Blood samples were taken at 1,3,6 and 12 months of HU. Hemoglobin and Hct increased from 3rd month of therapy; RBC deformability increased from 1 month onwards - effects more pronounced in non α-gene deletion. The blood viscosity did not change in SCA patients receiving HU therapy, which is important as increased viscosity increases the frequency of VOC in SCA. Also implications for possible use of HU in other sickle syndromes e.g. SC disease, which have increased blood viscosity compared to SCA.

Changing practice: red blood cell typing by molecular methods for patients with sickle cell disease

Casas et al, 2015 Transfusion

Link to abstract: http://onlinelibrary.wiley.com/doi/10.1111/trf.12987/abstract

Retrospective study of RBC antigen phenotypes and genotypes, as per pre-transfusion samples done routinely at 1 year of age. Compared RBC antigen phenotypes obtained by hemagglutination methods and by genotyping predictions. Genotyping was done using DNA-based assays targeting SNP associated with blood group Ag expression for 35 antigens.

494 patients (single-institution (CHOP), 2008-2014), total 6360 antigen comparisons; Results: 77 discrepancies (1.1%): 16 Fyb, 13 Jkb, 10 M, 10 N, 7 S. Serologic assays were redone for 66; 64 in concordance with genotyping –> concordance 0.9997. 34 false-positive serologic testing; 33 false-negative serologic testing and 15 false negative serologic results associated with alleles encoding weak antigens or single-dose Fyb expression.

Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study.

Inaba et al (2015) Blood

Link to abstract: http://www.bloodjournal.org/content/126/13/1575

This international retrospective study (including COG, St Jude's, and BFM data) included 490 patients (age ≤18 years) with non–Down syndrome AMKL diagnosed from 1989 to 2009. This AML subtype occurred in 7.8% of pediatric AML. Five-year event-free (EFS) and overall survival (OS) were 49.0% ± 2.7% in the cohort from 2000 to 2009 - significantly lower than for other AML subtypes. It was noted that patients treated in 2000 to 2009 received higher cytarabine doses and had better EFS and OS than those diagnosed in 1989 to 1999. The authors classified AMKL into 3 risk groups based on cytogenetics:

- Good risk—7p abnormalities (5 year EFS 74%, 5 year OS 77%)
- Intermediate risk—others including t(1;22)(p13;q13)/OTT-MAL (RBM15-MKL1) and 11q23/MLL except t(9;11). (5 year EFS 50%, 5 year OS 56%)
- Poor risk—normal karyotypes, –7, 9p abnormalities including t(9;11)(p22;q23)/MLL-MLLT3, –13/13q-, and –15 (5 year EFS 22%, 5 year OS 24%)

This risk stratification might help tailor treatments to each subgroup better.

Outcome of relapsed infant acute lymphoblastic leukemia treated on the interfant-99 protocol.

Driessen et al (2015) Leukemia

Link to abstract: http://www.nature.com/leu/journal/vaop/naam/abs/leu2015246a.html

Infant ALL is known to have high relapse rate, but published data on the outcome of relapsed infant ALL is limited. This paper report on clinical outcome of infant ALL patients who relapsed in the Interfant-99 study (202 out of 478 patients). Median follow up 5.2 years (1 month – 10 years).

159 patients (78.7%) received relapsed treatment with curative intent, 87 underwent HSCT. The 3-year OS was 24.9%. For prognostic factors, young age, high WBC count at initial diagnosis, early relapse (within 2 years from initial diagnosis), and BM involvement were associated with inferior outcome. Comparison on treatment by chemotherapy alone vs HSCT showed advantage of HSCT for patients who had early relapse, but no advantage for patients who relapsed later.

Authors concluded that relapsed infant ALL was not invariably lethal, treatment with curative intents and new therapeutic strategies may be beneficial.

Unrelated cord blood transplantation for childhood acute myelogenous leukemia: the influence of cytogenetic risk group stratification.

Michel et al (2015) Leukemia

Link to abstract: http://www.nature.com/leu/journal/vaop/naam/abs/leu2015243a.html

The authors aim to look at results of UCBT in childhood AML according to cytogenetic risk group stratification and disease status at time of transplant. The study included 293 patients with AML, who received single unit UCBT. For time of transplant, 114 in CR1, 133 in CR2, 46 had more advanced phase of disease. Median follow up 49 months. According to karyotype, patients classified into favorable, intermediate and unfavorable groups. They concluded that the best results were achieved for patients with unfavorable karyotype in CR1 (DFS 73%) and favorable karyotype in CR2 (DFS 67%).

Biomarkers for Diagnosis and Prognosis of Sinusoidal Obstruction Syndrome after Hematopoietic Cell Transplantation.

Akil A et al (2015) Biology of Blood and Marrow Transplantation

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/26172478

In this study, candidate protein biomarkers of SOS (VOD) were identified using a quantitative mass spectrometry–based proteomics approach by comparing plasma pooled from 20 patients with and 20 patients without SOS. Six proteins were selected and then evaluated for diagnostic potential on samples from 80 patients with five more proteins, which were selected from the literature. The results identified a suggestive biomarker panel for diagnosis of SOS measured as early as on the day of transplant showing >80% correct prediction of SOS onset.

Ceritinib in patients with advanced anaplastic lymphoma kinase–rearranged anaplastic large-cell lymphoma

Richly et al, 2015 Blood

Link to abstract: http://www.bloodjournal.org/content/126/10/1257

Ceritinib is a novel, selective ALK inhibitor, which has been shown to induce complete tumor regression of crizotinib-resistant xenograft models of ALK+ ALCL. This study reported on 3 patients with ALK+ ALCL relapse who received Ceritinib on a phase I dose escalation trial as part of an expansion cohort of 304 patients with ALK+ve tumors (ASCEND-1 trial). Two patients achieved a complete response (CR) and 1 had a partial response (PR, 94.8% tumor reduction). Response was seen for at least 20 months in all treated patients. This outlines Ceritinib as a potential agent in ALK+ ALCL.

A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A COG phase 1 consortium study (ADVL1011).

Loh ML et al, 2015 Pediatric blood and cancer

Link to abstract: http://onlinelibrary.wiley.com/doi/10.1002/pbc.25575/abstract

Phase 1 study including >12 m/o to <22 y/o with recurrent/refractory solid tumors (including lymphoma), or relapsed/recurrent ALL, AML or MPN. Ruxolitinib (JAK1/2 inhibitor) given BID x 28 days/cycle. Forty-nine patients enrolled, 28 ST in dose escalation component (27 evaluated), 17 leukemia pts, 4 with MPN (10/21 evaluated). Median of 1 cycle given. 5 patients had dose limiting toxicity (nausea/vomiting, neutropenia, elevated CK, elevated Cr with AKI). In ST pts, 4/27 pts had grade 4 hematologic toxicity on cycle 1 (lymphopenia, neutropenia), 2/36 cycles with grade 4 hematologic toxicity on subsequent cycles (lymphopenia, thrombocytopenia). In all pts, 1/37 with grade 4 non-hematologic toxicity in cycle 1 (elevated ALT), 1/36 pts on subsequent cycles with grade 4 non-hematologic toxicity (elevated AST).

No objective response in ST pts. 12/37 pts with stable disease after cycle 1 (8 ST pts, 4 hematologic malignancy pts). 1 pt with polycythemia vera had PR and got 18 cycles.

PK data – peak plasma concentration achieved 1 hour after first oral dose (range 1-4 hours), half-life 2.3±0.9 hours. Pharmacodynamics showed inhibition in vitro of JAK/STAT pathway. In vivo inhibition seen in 3 pre-B ALL patients, but not complete inhibition with dose studied. In pts with leukemia, none had JAK1/2 point mutation.

Bottom line – Ruxolitinib was well tolerated at all dose levels tested. No response seen, however only 1 patient enrolled in this trial (pt with PV) had a JAK mutation. May have more effect in pts with JAK mutations. Should be tested with chemotherapy in pts with JAK mutation.

Transmembrane TNF-α preferentially expressed by leukemia stem cells and blasts is a potent target for antibody therapy.

Zhou X et al, 2015 Blood

Link to abstract: http://www.bloodjournal.org/content/126/12/1433

Transmembrane tumor necrosis factor-α (tmTNF-α) in leukemia is preferentially expressed in leukemia cells of human bone marrow samples with AML (n = 69), B- or T-ALL (n = 30) compared to non-malignant anemia (n = 30). TmTNF-α+ expression seemed to correlate with poor prognosis. Knockdown of tmTNF-α+ expression rendered leukemia cells more sensitive to chemotherapy in vitro and delayed regeneration of leukemia in a mouse model. These mice transplanted with leukemia cell lines were treated with a monoclonal antibody targeting tmTNF-α. This resulted in leukemia cell killing via antibody-dependent cell-mediated and complement-dependent cytotoxicity in vitro and inhibited leukemia cell growth in vivo while simultaneously sparing normal hematopoietic cells.

TmTNF-α represents a novel target antigen in acute leukemia.

Disease evolution and outcomes in familial AML with germline CEBPA mutations.

Tawana K et al, 2015 Blood

Link to abstract: http://www.bloodjournal.org/content/126/10/1214

24 individuals from 10 families with CEBPA germline mutations and AML had whole-exome (WES) and deep sequencing on leukemic cells. The results showed that germline CEBPA mutations clustered within the N-terminal and were highly penetrant, with AML presenting at a median age of 24.5 years (range, 1.75-46 years). In all diagnostic tumors tested (n = 18), a

second CEBPA mutation was detected, with the acquired (somatic) mutations preferentially targeting the C-terminal. Deep sequencing of diagnostic and relapse paired samples suggested that recurrence was triggered by novel, independent clones with different CEBPA mutations than at presentation. The cumulative incidence of relapse in patients with this syndrome was 56% at 10 years (n = 11), and 3 patients experienced ≥3 disease episodes over a period of 17 to 20 years; still, long-term overall survival was favorable (10-year overall survival, 67%).

In conclusion, this article states that relapse in patients with germline CEBPA mutatuion is due to additional novel mutations and not recurrence of the initially seen one and that treatment for relapse might therefore be more successful than in other types of leukemia as shown by the relatively good survival rate.

Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies.

Scott D et al, 2015 Journal of Clinical Oncology

Link to abstract: http://jco.ascopubs.org/content/33/26/2848.long

Diffuse Large B-Cell Lymphoma (DLBCL) can be classified into 2 distinct subtypes depending on the stage of development of B-cells using gene expression analysis: germinal center B-cell–like (GCB) and activated B-cell–like (ABC) subtypes. These groups have distinct biology and treatment outcome. In adult oncology most clinicians still use International Prognostic Index (IPI) score and MYC/BCL2 co-expression status in routine practice to prognosticate, as the requirement for fresh frozen biopsies and microarray technology to determine sub-group seemed insurmountable.

In this paper the authors compared these "old-fashioned" markers to a recently described gene expression-based assay, the Lymph2Cx assay. The Lymph2Cx assay can be applied to formalin fixed tissue and has been shown to be highly accurate and concordant in sub-group assignment between laboratories. The authors applied the assay to pretreatment FFPE biopsies from 344 patients (>16 years) with de novo diffuse large B-cell lymphoma (DLBCL) uniformly treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) at the British Columbia Cancer Agency.

They found that patients with activated B-cell–like DLBCL had significantly inferior outcomes compared with patients with germinal center B-cell–like DLBCL and that this was independent of IPI score and MYC/BCL2 immunohistochemistry. Could similar technology be used in children with DLBCL to prognosticate (in particular in the AYA population) and to drive trial questions?

CD200/BTLA deletions in pediatric precursor B-cell acute lymphoblastic leukemia treated according to the EORTC-CLG 58951 protocol

Ghazavi, F (2015) Haematologica

Link to abstract: http://www.haematologica.org/content/100/10/1311

CD200 and BTLA recurrent deletions (on 3q13.2) were screened for in 1154 patients (<18 years old) with high-risk precursor B-ALL treated with the EORTC-CLG 58951 protocol and identified in 4.8%. They are strongly associated with ETV6-RUNX1 translocations. CD200/BTLA deletion was associated with higher proportion of positive MRD at end of induction and inferior event free survival (70.2% vs 83.5%) and poorer disease free survival (72.8% vs 84.4%), but not overall survival (91% vs 87%) at 8 years compared to those without deletion. The highest number of patients with this mutation, were in the poor prognosis group (as per EORTC-CLG classification). Multivariate analysis indicates the deletion of CD200/BTLA as an independent prognostic factor on EFS. This has an implication for disease stratification and therapeutic planning – contextualizes relapsed disease though no prospective testing of intensified therapy.

Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes

R Peffault de Latour (2015) Bone Marrow Transplantation

Link to abstract: http://rdcu.be/ejjI

This report summarizes the recommendations for transplanting children with IBMF including indications for HSCT, timing, stem cell source and conditioning regimen for inherited bone marrow failure syndromes. HSCT remains the only curative treatment option for disturbances of

hematopoiesis in IBMFS. Prospective international clinical trials are urgently required in order to enhance the management of these rare disorders, and in time, lead to improved outcomes.

Efficacy of Retinoids in IKZF1-Mutated BCR-ABL1 Acute Lymphoblastic Leukemia

Churchman et al (2015) Cancer Cell

Link to abstract: http://www.cell.com/cancer-cell/abstract/S1535-6108(15)00268-8

Multiple methods were used in mouse models and human-derived cell cultures to reach the following findings:

- IKZF1 and Arf mutations confer lymphoid stem cell lineage in Ph+ cells. Ph+ cells in the absence of IKZF1 mutations are much more likely to develop into a myeloid phenotype.
- IKZF1 mutations increase the adhesiveness of leukemia cells and this increases their ability to adhere to the bone marrow niche.
- Mice with Ph^{+}/$IKZF1^{+/-}$ or combined with other Ikaros-related downstream mutations had a poorer survival with dasatinib therapy than Ph^{+} with wild type IKZF1
- Retinoids improved the response to dasatinib in in vitro assays as well as in the mouse model and was better than a combination of dasatinib with conventional chemotherapy (in mice with Ph+ and an Ikaros mutation).

Childhood and Adolescent nodular lymphocyte predominant Hodgkin lymphoma – A review of clinical outcome based on the histological variants

Shankar et al (2015) British Journal of Haematology

Link to abstract: http://onlinelibrary.wiley.com/doi/10.1111/bjh.12055/abstract

Retrospective data collection, with pathological review of 60 biopsies (CCLG, Euronet PHL-LP1, OK Children's Cancer Study Group HD3) between 2001 and 2014. Aim to evaluate treatment outcome in patients with histopathological variants of nodular lymphocyte predominant HL

(nLPHL) after de-escalation of therapy. Patients: 5-16 years (med: 14y.o.); 47 with typical (nLPHL), 13 with variant nLPHL. 14 were treated with excision alone; 46 treated with chemo (40 CVP, 16 other regimens).

Compared to nLPHL, variant nLPHL is associated with lower complete response rates (CCR: 46% vs 81%) p = 0.029. There were trends seen which were not significant: Higher stage at diagnosis (stage III: 23% vs 6%) and increased risk of relapse (15% vs 4%).

Risk factors and timing of relapse after allogeneic transplantation in pediatric ALL: for whom and when should interventions be tested?

Pulsipher et al (2015) Bone Marrow Transplantation

Link to abstract: http://rdcu.be/ejjj

The study looked at the effect of established leukemia disease risk-classification groups, pre- and post-HCT MRD detection, and the occurrence of GvHD on relapse and survival reviewing COG protocol ASCT0431 from 2007 to 2011 including 105 patients. Pre-HCT MRD <0.1% and aGvHD by day +55 were associated with decreased relapse and improved event-free survival (EFS). Patients with pre-HCT MRD <0.1% who did not experience aGvHD had higher rates of relapse than those who did develop aGvHD (40% vs 13%; P = 0.008).

The population at highest risk of poor outcome was HR CR1/CR2 patients who were MRD+ pre-HCT who then did not experience grade I–III aGvHD (EFS 12%). 59% of all relapses occurred between days +100 and +400 in patients without aGvHD.

This analysis clarifies that both pre-HCT and post-HCT factors (disease risk, pre- and post-HCT MRD and aGvHD) can be used to define populations with poor outcome. An optimal window to initiate intervention to prevent relapse occurs between day +55 and +200 after HCT. Study of interventions with maintenance courses of immunotoxins or weaning immune suppression followed by agents designed to enhance anti-tumor effect may prevent relapse in appropriately defined high-risk populations.

The potential of clofarabine in MLL -rearranged infant acute lymphoblastic leukaemia.

Stumpel et al (2015) European Journal of Cancer

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/?term=clofarabine+stumpel

MLL-rearranged acute lymphoblastic leukaemia (ALL) in infants is the most difficult-to-treat type of childhood ALL, displaying a chemotherapy-resistant phenotype, and unique histone modifications, gene expression signatures and DNA methylation patterns. Clofarabine effectively targeted primary MLL-rearranged infant ALL cells in vitro at the lowest concentrations, Interestingly, clofarabine displayed synergistic cytotoxic effects in combination with cytarabine. Higher concentration of clofarabine induced demethylation of the promoter region of the tumour suppressor gene FHIT (Fragile Histidine Triad), a gene typically hypermethylated in MLL-rearranged ALL. Clofarabine might be a good candidate in combination with standard chemotherapy treated high-risk infant leukemia as cytotoxic and epigenomic modifier.

Tuning Sensitivity of CAR to EGFR Density Limits Recognition of Normal Tissue While Maintaining Potent Antitumor Activity.

Caruso et al (2015) Cancer Research

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/26330164

Affinity-Tuned ErbB2 or EGFR Chimeric Antigen Receptor T Cells Exhibit an Increased Therapeutic Index against Tumors in Mice

Liu et al (2015) Cancer Research

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/26330166

Both of these groups published similar results in the same issue. One of the problems with CAR-T cells is that they can be engineered to detect a variety of tumor-related antigens but many of these, such as EGFR, are also present on normal tissues and this leads to toxicity. Both

groups tested antigen receptors with high affinity for EGFR against those with moderate affinity. Those with high affinity targeted tumor and normal tissue but the moderate affinity ones targeted mostly only tumor tissue and left normal tissue alone.

Patients With Proneural Glioblastoma May Derive Overall Survival Benefit From the Addition of Bevacizumab to First-Line Radiotherapy and Temozolomide: Retrospective Analysis of the AVAglio Trial

Sandmann T et al, 2015 Journal of Clinical Oncology

Link to abstract: http://jco.ascopubs.org/content/early/2015/06/24/JCO.2015.61.5005.abstract

The previously reported AVAglio (Avastin in Glioblastoma) trial found prolonged progression-free survival (but not overall survival) in adult patients with GBM who had bevacizumab added to radiotherapy plus temozolomide. This paper is a follow up from that study and looks to determine if certain sub-groups may actually have an OS benefit from adding avastin to first line standard of care. The authors retrospectively grouped pre-treatment specimens from just over a third of patients enrolled in the study (349/921) using gene expression analysis and IDH1 mutation status. They found that bevacizumab conferred an OS advantage versus placebo in patients with proneural *IDH1* wild-type tumors (17.1 *v* 12.8 months, respectively; hazard ratio, 0.43; 95% CI, 0.26 to 0.73; *P* = .002).

Take home message: With IDH1 mutations seen in 7 of 43 pediatric primary malignant gliomas treated on the Children's Oncology Group ACNS0423 study (and therefore 36 of 43 WT) it will be interesting/important for us to see if this is validated when the results of the HERBY study are reported (see https://clinicaltrials.gov/ct2/show/NCT01390948).

Phase 1 study of Birinapant, a novel SMAC mimetic. Inhibitors of apoptosis (IAP) proteins suppress apoptosis and activate TNF. Overexpression of IAP contributes to tumor chemotherapy resistance. SMAC binds to IAP causing them to degrade and apoptosis to occur in tumor cells.

Amaravadi et al, 2015 Molecular Cancer Therapeutics

Link to abstract: http://mct.aacrjournals.org/content/early/2015/09/02/1535-7163.MCT-15-0475.abstract?sid=a5c93016-4afe-43a8-9272-369a40095dc3

Phase 1 study of Birinapant, a novel SMAC mimetic. Inhibitors of apoptosis (IAP) proteins suppress apoptosis and activate TNF. Overexpression of IAP contributes to tumor chemotherapy resistance. SMAC binds to IAP causing them to degrade and apoptosis to occur in tumor cells.

This is the first human study of birinapant. In 50 adults this drug was well tolerated with main side effects of headache, nausea and vomiting. These were patients with relapsed or refractory colorectal, head and neck, lung, and pancreatic cancers, soft tissue sarcomas and melanomas aged 31-58. The regimen was given iv q 3 weeks, with good PK and PD profile. Transient cytokine release syndrome seen at doses which exceeded the MTD. Stable disease and anti-tumor activity was noted.

Further studies will look at combination with other chemotherapy (particularly as it can overcome resistance), and is in phase 2 trials for MDS and ovarian cancer.

Durability of Kinase-Directed Therapies—A Network Perspective on Response and Resistance.

Murray et al, 2015 Molecular Cancer Therapeutics

Link to abstract: http://mct.aacrjournals.org/content/14/9/1975.abstract?sid=b737b689-2fe8-4813-95b7-d36f1bafd756

Protein kinase directed cancer therapies are being used more and more, but have issues with poor clinical response ("innate resistance") or disease relapse ("acquired or secondary resistance). Examples of these drugs are: sunitinib, dabrafenib, erlotinib, crizotinib and imatinib. This is a review of intrinsic and extrinsic mechanisms of resistance to these drugs and how drug combination therapy can be used to improve outcomes.

Real-time Imaging of the Resection Bed Using a Handheld Probe to Reduce Incidence of Microscopic Positive Margins in Cancer Surgery.

Erickson-Bhatt et al, 2015 Cancer Research

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/26374464

This group developed a handheld probe that uses Optical Coherence Tomography (OCT) to try to differentiate between malignant and normal tissue in a surgical bed and a resection specimen (based on how organized the tissue appears) in an attempt to guide the surgeon as to the extent of resection. They tested the device in 35 breast surgery cases but did not suggest a change in management based on the findings. Histological assessment of the resection specimen was used as the gold standard. The sensitivity and specificity of this device for detecting positive margins were 91.7% (62.5% - 100%) and 92.1% (78.4% - 98%) respectively.

ABCG2 Transporter Expression Impacts Group 3 Medulloblastoma Response to Chemotherapy.

Morfuace et al, 2015 Cancer Research

Link to abstract: http://www.ncbi.nlm.nih.gov/pubmed/26199091

ABC membrane transporters have been implicated in several tumors as conferring chemotherapy-resistance by expelling the drug from the cell. Group 3 medulloblastoma is known to be particularly difficult to treat with current therapy. This group showed that ABC group 2 transporters have increased expression in both human and mouse group 3 medulloblastoma cells and this expression decreased in vitro response to 11/12 chemotherapeutic agents. In a mouse model they showed that blockade of ABCG2 using Ko143 increased tumor susceptibility to topotecan and the combination of these two drugs produced the longest survival time (compared to each individually).

Spatiotemporal Evolution of the Primary Glioblastoma Genome.

Kim et al, 2015 Cancer Cell

Link to abstract: http://www.cell.com/cancer-cell/abstract/S1535-6108(15)00265-2

Kim et al examined 38 pairs of primary and relapsed GBMs using CGH-array, whole exome sequencing, and RNA Seq. They found that distant relapses had a much more divergent mutation profile compared to local relapses. It has also been previously known that IDH1 mutant tumors (usually progressed from LGG) have a hypermutation profile at relapse if initially treated with temozolamide. Kim et al confirmed this finding but also found that it does not hold true for IDH1 wild type tumors. You can read an excellent summary of this paper in the same issue by Vijay Ramaswamy and Michael Taylor (see http://www.cell.com/cancer-cell/abstract/S1535-6108(15)00301-3).

Intestinal Obstruction in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

Madenci A et al, 2015 Journal of Clinical Oncology

Link to abstract: http://jco.ascopubs.org/content/early/2015/08/06/JCO.2015.61.5070.abstract

This report from the Childhood Cancer Survivorship (retrospective cohort) study looked at the cumulative incidence of intestinal obstruction requiring surgery occurring 5 or more years from cancer diagnosis in 12,316 5-year survivors (2,002 with and 10,314 without abdominopelvic tumors) and compared this to 4,023 sibling participants. They found the cumulative incidence to be 5.8% among survivors with abdomino-pelvic tumors, 1.0% among those without abdomino-pelvic tumors, and 0.3% among siblings. They also found that developing late intestinal obstruction increased subsequent mortality among survivors.

Take home message: we need to promote awareness of this complication among patients in our long term follow up service, particularly those with abdomino-pelvic tumors.

The utility of computed tomography in the management of fever and neutropenia in pediatric oncology

Rao et al, 2015 Pediatric Blood and Cancer

Link to abstract: http://onlinelibrary.wiley.com/doi/10.1002/pbc.25561/abstract

Retrospective cohort study including oncology patients admitted with F&N from 2003-2009, ≤21 years. Median duration of admission was 5 days (range 0-79), 22% of patients had a CT scan (139 scans in 93 individuals). 21% of those who had a scan had multiple scans during the admission. 68% of scans included chest, 69% included abdomen, 41% included head, & 55% pan-scans (>1 body part).

Risk factors for having a scan: older age (≥7 years), longer admission (≥7 days), positive culture from non-blood source, findings on CXR, additional disease burden ("sicker" patients, not well defined) or symptoms in addition to F&N at presentation.

Pan-scans more likely in younger patients (<7 years), pts with hematologic malignancy, history of fungal infection, +ve blood cultures or +ve viral PCR, pts without additional symptoms beyond F&N.

66% of scans identified possible source of infection – sinusitis (27%), pulmonary infiltrate (27%), possible fungal lesions (17%). Factors associated with finding infection: African American race, hypotension, chest CT alone, head CT alone or included in pan-scan, scan done ≥7 days after admission.

In 41%, CT led to a change in management, most often change in antibiotic (53%) or antiviral/antifungal (42%). Pan-scans seemed not more effective, abdominal scan were good at ruling out infection but not good to identify infection (i.e. usually not helpful).

Alignment of Do-Not-Resuscitate Status With Patients' Likelihood of Favorable Neurological Survival After In-Hospital Cardiac Arrest

Fendler et al (2015) Journal of the American Medical Association (JAMA)

Link to abstract: http://jama.jamanetwork.com/article.aspx?articleid=2442939

This study involved 26 327 adult patients who had recovery of circulation after in-hospital cardiac arrests at 406 US hospitals between April 2006 and September 2012. The authors used a validated prognostic tool to calculate each patient's likelihood of survival without severe neurological disability. They looked at the association between good neurological survival and having a post-arrest Do-Not-Resuscitate (DNR) order written.

22.6% [95% CI, 22.1%-23.1%] of the patients had a DNR order written within 12 hours of return of circulation. These were older and sicker patients, and were more likely to have a worse neurological prognosis. However, even amongst the patients with the poorest prognosis (less than a 10% chance of a favorable neurological survival) only 1/3 had a DNR order, reasons were not assessed.

Interestingly, patients with a good prognosis who somehow ended up with a DNR, ended up using lower levels of resources and had worse outcomes in the long term than those with a good prognosis who didn't get a DNR.

Cardiometabolic Risks and Severity of Obesity in Children & Young Adults

Skinner et al (2015) New England Journal of Medicine

Link to abstract: http://www.nejm.org/doi/full/10.1056/NEJMoa1502821

This is a cross-sectional analysis of data from a US population based study - the National Health and Nutrition Examination Survey between 1999 and 2012. They looked at the relationship between obesity and a number of cardiometabolic risk factors. 8579 children and young adults in this survey were overweight or obese. Within this group, the more obese, the higher the

risks of negative cardiometabolic risk factors like high BP, negative cholesterol and lipid profiles. This is a general population study – not specific to childhood cancer survivors.

Journal of Clinical Oncology Special Series Issue on collaborative efforts in childhood cancers and survivorship.

September 2015 Journal of Clinical Oncology

Link to abstract: http://jco.ascopubs.org/content/33/27

The Journal of Clinical Oncology September 20, 2015 is a MUST read. This special edition details the collaborative efforts that have contributed to the advances in survival for childhood cancers:

- Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration
- Collaborative Efforts Driving Progress in Pediatric Acute Myeloid Leukemia
- Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead
- Pediatric Hodgkin Lymphoma
- Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape
- Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration
- Advances in Risk Classification and Treatment Strategies for Neuroblastoma
- Pediatric and Adolescent Extracranial Germ Cell Tumors: The Road to Collaboration
- Osteosarcoma: Current Treatment and a Collaborative Pathway to Success
- Ewing Sarcoma: Current Management and Future Approaches Through Collaboration
- Rare Tumors in Children: Progress Through Collaboration
- Collaborative Research in Childhood Cancer Survivorship: The Current Landscape
- Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global Challenge

Sensitivity of the Automated Auditory Brainstem Response in Neonatal Hearing Screening.

Levit et al, 2015 Pediatrics

Link to abstract: http://pediatrics.aappublications.org/content/136/3/e641.abstract

This article investigated the sensitivity of the auditory brainstem response (ABR) test to identify hearing loss. A cohort of infants who failed the initial screening otoacoustic emissions test (TEOAE), or were admitted to the NICU for more than 5 days, were referred for further testing with the ABR. 24% of the infants who passed the ABR were later diagnosed with hearing loss, which represented more than 50% infants in the cohort who were diagnosed with hearing loss. This study highlights the need for regular auditory testing and need for continued improvement of the sensitivity of the ABR.