Thursday, June 22, 2023

Session I - Oncology

MICRORNA AS CELL DEATH REGULATOR AND LIQUID BIOPSY MARKER IN PEDIATRIC GB

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Glioblastomas (GB), represent the highest grade of gliomas, which are aggressive lethal brain tumors both in children and adults. The current multimodal therapy includes surgery, chemotherapy, and radiotherapy. Clinical, molecular, genetic, and biologic data reveal significant differences between the pediatric and adult GB tumors. Regardless of age, current therapies are not efficient and survival is very poor. Moreover, in pediatric GB-patient's therapies can cause severe neurotoxicity to the developing brain, further complicating the already significant morbidity in children. Therefore, there is a great need for better understanding of pathogenesis, new prevention opportunities and novel therapies for pediatric GBM. Increasing evidence supports important role of MicroRNAs (miRNAs) in cancer because of their concurrent post transcriptional expression regulation of multiple genes. We examined MirRNAs that their expression is altered in pediatric GB. We confirmed that those miRNAs expression are also elevated/ suppressed in pediatric cell lines compared to normal astrocytes. MiRNAs silencing/ mimicing in pediatric GBM cell lines resulted in decrease cell viability and colony formation compared to non- treated cells and it also reduced their migration and invasion capacity. Moreover, we were able to detect those altered miRNAs in the blood of pediatric GB for a novel liquid biopsy marker.

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ETHNIC AND SOCIOECONOMIC DISPARITIES IN SURVIVAL OF CHILDREN AND ADOLESCENTS WITH CNS TUMORS IN SOUTHERN ISRAEL

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Background: This study sought to evaluate survival of pediatric and adolescent patients with central nervous system (CNS) cancer in southern Israel, outline disparities between ethnic and socioeconomic groups (Bedouin Arabs compared to Jews) and evaluate the role of socioeconomic status (SES) in ethnic disparities.
Methods: A retrospective study was conducted among 91 patients aged one to 20 years, who were diagnosed with CNS tumors between 2001 and 2017, and followed-up through 2020. Ethnic differences in survival were measured by age, sex, stage, histology and SES. One and 3-year survival rates were calculated. Multivariable regression analysis was used to estimate adjusted ethnic differences in survival rates.
Results: Ethnic differences in survival existed within all studied variables. All Bedouin patients lived in low SES settlements (All Bedouin settlement in Southern Israel are ranked in lower socioeconomic deciles). Twenty-eight patients had medulloblastoma. Seven (25%) presented with leptomeningeal disease or distant metastases. Medulloblastoma molecular subgroups were not assessed for logistic reasons. Three-year overall survival of Bedouins was 50% compared to 92.3% for Jews. Adjusted risk of death at 3 years was significantly higher for Bedouin patients (aHR 3.36, 95% CI 1.41-7.98, P = .006).
Conclusions: We conclude that Bedouin children with CNS tumors have significantly lower survival rates compared to Jewish children, and SES seems to play a major part in these disparities. Factors influencing these disparities should be addressed and public health interventions to eliminate these disparities should be developed.

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Session II – Oncology

REVACCINATION OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA FOLLOWING COMPLETION OF CHEMOTHERAPY

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Background: Intensive chemotherapy has a significant impact upon humoral immunity, yet there are no uniform guidelines for post-chemotherapy vaccinations.

Objectives: The immunity to measles, varicella, polio, pertussis, HAV & HBV among previously vaccinated children who completed ALL therapy was evaluated as well as the utility of revaccination in patients with insufficient antibody titers.

Methods: Serum antibody levels were assessed 3-6 months after completion of AIEOP BFM ALL 2009 chemotherapy. Children who did not have sufficient antibody titers to specific agents were revaccinated with a single dose accordingly. Antibody levels were assessed at least 4 weeks after revaccination.

Results: Ninety-six children were recruited. Seventeen (18%) recieved HR arm.

The majority of children (96%) did not have protective antibody levels to at least one of the vaccine-preventable diseases. There were significant differences between the different types of vaccines with regard to the incidence of post-treatment pre-booster protective antibody levels. The highest percentage of protective antibody level was against polio (87%) and the lowest against pertussis (4%) ($P<0.001$).

There were significant differences in antibody seronegativity rates between HR and non HR patients for the following vaccines: measles (100% vs 48%, $p = 0.012$), HBV (92 % vs 61%, $p = 0.031$), and HAV (92 % vs 47%, $p = 0.004$). Seronegativity rates were higher for the HR group for the other vaccines as well, without statistical significance. The response after administering a booster dose was highest for varicella and polio (100%) and lowest for pertussis booster (36%).

Conclusions: Loss of humoral protection for vaccine-preventable diseases is common. Revaccination with a single vaccine dose is beneficial in 34%-100%, depending on the type of vaccine. We recommend this revaccination schedule to all previously vaccinated children upon completion of ALL therapy.

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Session III - Hematology

GENETIC BACKGROUND AND CLINICAL CHARACTERISTICS OF CONGENITAL NEUTROPENIAS IN ISRAEL

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Background. Congenital neutropenias are a heterogenous group of disorders characterized by severe infections and a high risk of myeloid transformation, with variable causative genes in different ethnicities. The Israeli population is unique due to its ethnic variability and a high rate of consanguinity, therefore, we aimed to evaluate the national clinical and genetic spectrum of patients with congenital neutropenias.

Procedures. Our cohort included patients diagnosed with congenital neutropenias from the Israeli Inherited Bone Marrow Failure registry. Sanger sequencing was performed for *ELANE* or *G6PC3* and patients with wild-type *ELANE/G6PC3* were referred for next generation sequencing.

Results. Overall, 65 patients were diagnosed with neutropenia. Thirty-four of 51 patients (66.6%) with severe congenital neutropenia were genetically diagnosed, of those, the most commonly mutated gene was *ELANE* (44%). A large percentage had biallelic mutations in *G6PC3* (26%) all of consanguineous Muslim Arab origin. Other genes involved were *SRP54, JAGN1, TAZ* and *SLC37A4*. Seven patients had cyclic neutropenia, all with mutations in *ELANE* and 7 had Shwachman-Diamond syndrome caused by biallelic *SBDS* mutations. Eight patients (12.3%) developed myeloid transformation. Interestingly, these include 6 patients with an unknown underlying genetic cause. Nineteen (29.2%) patients underwent hematopoietic stem cell transplantation, most often due to

insufficient response to treatment with granulocyte-colony-stimulating-factor or due to myeloid transformation.

Conclusions. The prevalence of genes causing congenital neutropenias in Israel is unique with a high prevalence of mutations in *G6PC3* and an absence of patients with *HAX1* mutations. Similar to other registries, for 26.1% of the patients a molecular diagnosis was not achieved, however myeloid transformation was common in this group, emphasizing the need for a close follow-up.

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LONG TERM HEMATOPOIETIC DYSFUNCTION IN PATIENTS WITH LARGE-SCALE MITOCHONDRIAL DNA DELETION SYNDROMES

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Pearson syndrome (PS) is the only single large-scale mitochondrial DNA deletion (SLSMD) syndrome presenting with hematologic abnormalities, usually a severe though transient cytopenia of childhood. Recently, progression to myeloid malignancies was described among PS patients. No hematologic dysfunction is noted in older PS, or SLSMD patients presenting at mature ages, whether as Kearns–Sayre syndrome (KSS) or with progressive external ophthalmoplegia (PEO). Since the underlying mitochondrial DNA deletion is similar in all SLSMDs, we hypothesized that bone marrow (BM) dysfunction is a common and persistent manifestation in these patients.

We studied 16 SLSMD patients: 13 were diagnosed with PS, and three with KSS. The median age at diagnosis was 25 months (range 2-136 months). Seventy-five percent of patients presented with cytopenia in infancy, and 56% required blood products. Resolution of cytopenia occurred in 92% of these patients, at a median age of 24 months (range 12-39 months).

BM studies were performed in all patients, and 56% of them had multiple BM evaluations. All BM biopsies examined showed marrow dysfunction signs, including in patients without cytopenia. Median BM cellularity was 50% (range 30-80%) at a median age of 60 months. Marrow samples showed a paucity of precursor myeloid cells, signs of dyserythropoiesis, and abnormal or missing megakaryocytes. The median CD34+ count was 0.68% (range 0.27-1.92%), compared to the 1-2% expected. BM colony formation unit (CFU) capacity was reduced in SLSMD patients; median CFU of 280/10^6 cells compared to 1090/10^6 cells in healthy controls (p=0.004). On cytogenetics, monosomy 7 was identified in 3/12 patients.

Long-term BM dysfunction is evident in all patients with SLSMD and includes a risk of developing clonal evolution and monosomy 7. This data, combined with other recent publications, highlights the ongoing marrow failure and suggests that SLSMD syndromes should be included under BM failure syndromes.

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RAS PATHWAY MUTATIONS IS THE DRIVER OF MDS IN A SUBSET OF PEDIATRIC PATIENTS

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The classification and diagnosis of hematological malignancies have been shifted in the recent years from morphological classifications to genetic ones. While most cases of pediatric acute myeloid leukemias are driven and classified by chromosomal translocations, a subset of cases are the consequence of serial acquisition of point mutations causing the malignant transformation. A single point mutation is usually not enough to drive acute leukemia or MDS, but specific mutations are known to be sufficient to drive a myeloproliferative disease like JAK mutations in myelofibrosis, PTPN11 mutations in JMML and KIT mutations in mastocytosis.

Pediatric MDS is less genetically classified. As more familial genetic predispositions syndromes are being discovered (GATA2, SAMD9, RUNX1. etc), many cases are found to originate from these germline mutations. Though two studies have published the genomic landscape of primary somatic MDS mutations, no molecular classification has been offered except the recent entity of UBTF-TD which might comprise up to 25% of MDS- excess blasts cases.

In this study we present 7 patients with pediatric MDS, which is driven by somatic RAS pathway mutations- mainly PTPN11. Though RAS pathway mutations are already known to present in pediatric MDS, based on the VAF, the mutual exclusivity with other class defining mutations, and the consistency of the mutation throughout follow up, we show that these mutations are the primary and sufficient event for the malignant transformation, as occurs in JMML. We hypothesize that this subset of cases shares a genetic background with JMML, while the phenotypic difference between JMML and MDS cases is probably linked to the cell of origin where the mutation occurred. While this is yet to be proved, we show that following mutational burden by NGS or dd PCR might serve as an MRD marker and direct therapeutic decisions.

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INCREASED PREVALENCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE I

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Congenital Dyserythropoietic Anemia Type I (CDA-I) is a rare disorder of erythropoiesis. All CDA-I patients are expected to suffer from iron overload and chronic hemolysis. Some patients with severe anemia may undergo splenectomy. Hemochromatosis, chronic hemolysis and splenectomy are all found to increase the risk for thromboembolism in thalassemic patients. As CDA-I patients have similar findings, we sought to evaluate the prevalence of thromboembolic events in these patients. We conducted a retrospective case-control study including 110 CDA-I patients (study group) and 326 age and sex-matched patients of the same ethnicity diagnosed with iron deficiency anemia (control group). We identified three cases (2.7%) with thromboembolic events in the CDA group and one case (0.3%) in the control group. All of them were female patients. Caprini risk assessment for venous thromboembolism was low to moderate for the three CDA patients and high for the IDA patient. When compared to the control group, patients with CDA-I were nine times more likely to develop a thromboembolic event (OR 9.11, 95% CI=1.15-185.27, p=0.057). All three CDA patients had a history of remarkable hemolysis and iron overload. Two of them underwent splenectomy. These findings show that CDA patients appear to be at increased risk for thromboembolic events.

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Session IV - Neuroblastoma

THE LANDSCAPE OF PERSISTER CELLS IN HIGH-RISK NEUROBLASTOMA

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Background: The mechanisms of high-risk neuroblastoma chemotherapy resistance remain largely unknown and the cells responsible for relapse have not been identified.
Aims: To discover, characterize, and target the cells responsible for relapse in high-risk neuroblastoma.
Methods: We used single nucleus RNA and bulk whole genome sequencing to identify and characterize the malignant cells that survive chemotherapy (persister cells) from a cohort of 20 matched diagnostic and definitive surgical resection high-risk neuroblastoma samples. Confirmatory functional studies using flow cytometry, qPCR, immunoblotting, CRISPR-CAS9 knock out, and small molecule inhibition were performed in eight representative cell lines derived from neuroblastomas at diagnosis and treated with standard-of-care chemotherapy.
Results: Five subtypes of persister cells were computationally identified through pathway-based clustering. Cycling persisters were abundant in two patients with early progressive disease. In contrast, most patients displayed a low number of cycling persisters, attributed to the suppression of *MYCN* activity, even in the presence of *MYCN* amplification. Two persister subtypes showed NFkB pathway activation, an observation that was recapitulated in a diagnostic PDX with *MYCN* amplification treated with chemotherapy. M2 macrophages were abundant in post chemotherapy specimens and displayed significant TGFβ expression, a known activator of NFkB signaling.
We validated our findings in *vitro*, confirming a decrease in both MYCN and/or MYC protein level as well as activation of NFkB signaling following chemotherapy, which was enhanced by co-culture with M2 macrophages. Pharmacologicinhibition of the NFkB pathway with the small molecule ML120B, a specific IkB kinase inhibitor, or genetic depletion of RelA using CRISPR-CAS9, both resulted in increased killing of persister cells when combined with chemotherapy.
Finally, we observe a significant upregulation of BCL-XL, a downstream effector of NFkB signaling in persister cells. Combination therapy of selective BCL-XL small molecule inhibitor A-1331852 with topotecan resulted in an 8.6-fold increase in cancer cell killing compared to topotecan alone ($p<0.0001$).

Conclusions: Cellular persistence is mediated by tumor cell-intrinsic and -extrinsic activation of NFkB signaling and BCL-XL expression. We are currently testing a BCL-XL-targeting PROTAC and expanding our efforts to define the immunopeptidome of persister cells.

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CIRCULATING TUMOR DNA TO GUIDE TARGETED THERAPY IN NEUROBLASTOMA

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Introduction: Neuroblastoma, an embryonic solid tumor of the peripheral sympathetic nervous system, is characterized by extensive intra-tumoral and stroma-derived heterogeneity. Tumors harbor pre-existing and acquired subclonal populations that are postulated to confer therapy resistance, and relapsed neuroblastomas demonstrate an increased proportion of somatic mutations, including enrichment of *ALK* and RAS-MAPK pathway activating mutations. Circulating tumor DNA (ctDNA) superiorly captures genetic tumor heterogeneity, and has potential to track clinical response and emergence of genetic mechanisms of resistance.

Methods: We profiled serial samples for circulating tumor DNA from patients enrolled on the NANT 1502 Phase I/IIb trial of lorlatinib using the commercially available Foundation Medicine ctDNA platform. We also developed a novel custom neuroblastoma-specific 23-gene ctDNA assay, and optimized panel design to detect MYCN and ALK amplifications, as well as ATRX deletions.

Results: Utilizing serial ctDNA assessments, we discovered acquisition of novel off-target resistance mutations in 27% of patients with relapsed/refractory high-risk neuroblastoma receiving lorlatinib therapy in the NANT 1502 study. These mutations occurred predominantly in the RAS-MAPK pathway. We also identified novel secondary compound mutations in ALK in 15% of patients, all acquired at disease progression, and functionally validated the effect of these mutations on lorlatinib resistance with cellular and biochemical assays.

With our custom ctDNA panel, we validated panel performance to a limit of detection of 0.5% variant allele frequency with 20 ng of ctDNA input. We demonstrate superior performance as compared with commercially available platforms, with increased detection of functionally relevant mutations predominantly in ALK and RAS-MAPK pathway genes. Utilization of this panel to profile serial ctDNA samples from patients enrolled on the current Phase III study is ongoing.

Conclusions: Our results establish the clinical utility of serial circulating tumor DNA sampling to track response and progression and to discover acquired resistance mechanisms. Our pediatric specific ctDNA panel demonstrates superior ability to detect mutations, and should be utilized to uncover genetic patterns of disease progression that can be leveraged to develop therapeutic interventions that overcome resistance.

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THE INFLUENCE OF IRINOTECAN ON CD47/PDL-1/GD-2 EXPRESSION IN NEUROBLASTOMA CELLS

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Background: Neuroblastoma is the most frequent extra-cranial solid tumor in children and only 50% High Risk patients survive at 5 years after diagnosis. Moreover, survivors suffer from long-term consequences of chemotherapy, surgery, and radiation therapy. Therefore, it is important to develop novel immunotherapeutic approach to combat High Risk Neuroblastoma in children. Neurobalstoma is known to have the ability to escape the immune system in several mechanisms. The 'Don't it me' signal by CD47, which inhibits macrophages, and the GD2, that inhibit T cells, and the PD1 receptor, that inhibits cytotoxic T cells, are involved in this immune escape. Irinotecan is a chemotherapy that has immunomodulatory effect in Neuroblastoma. The aim of this study was to assess the influence of irinotecan on expression of these molecules in Neuroblastoma cells.
Methods: The expression of CD47/PDL-1/GD-2 before and after treatment with irinotecan was tested using Sknbe and Shy Neuroblastoma cells. Phagocytosis assay was preformed using macrophages derived from PBMCs. Immunohistochemistry was done on tissue array using monoclonal antibody to CD47.
Results: We have found that the CD47 GD2 and PDL-1 receptors - are over expressed on Neuroblastoma cells. Interestingly, CD47 and PDL-1 expression were up regulated by treating the cells with irinotecan. Furthermore, upregulation of CD47 by irinotecan inhibited tumor cell phagocytosis by macrophages. Immunostaining for CD47 in tumor sections form Neuroblastoma patients revealed that CD47 was differentially overexpressed by Neuroblastoma tumors from different origin such as the adrenal, pelvic cavity, mediastinum, or the retroperitoneum.
Discussion: We therefore suggest that irinotecan could be used to overcome the immune escape of Neuroblastoma in conjunction with targeting CD47 in combination with PDL-1 and GD2.

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THE USE OF ANTI GD2 NAXITAMAB IN HIGH RISK NEUROBLASTOMA IN SHAARE ZEDEK MEDICAL CENTER

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Background: The use of anti GD2 antibodies in high risk neuroblastoma has proven to be effective, however it may be associated with significant side effects.
Aim: This study will present early experience with the anti GD2 antibody Naxitamab in a pediatric oncology center in Israel
Methods: Six patients received 67 cycles of Naxitamab in the Shaare Zedek Medical Center in Jerusalem between January 2022-January 2023. Data regarding patient medical background, treatment side effects and treatment efficacy was collected from patient files.
Results: Two patients were treated upfront with 2 cycles each as part of a compassionate use program. Four patients received a total of 63 cycles (8-20/patient). Median age was 9 years (range 4-26). Patients were treated at first line (2 patients) /refractory disease (1 patient) or relapse (3 patients following 7,9 and 10 lines of therapy consecutively). Six patients had grade 4 events outside pain. Grade 4 events included hypotension (2), severe desaturation (2), anaphylaxis and PRESS (1 each). One patient achieved complete response, 4 had partial response and one had progression.
Conclusion: Naxitamab is an effective therapy both at first line or in relapsed refractory disease. Safe administration despite significant life threatening side effects require collaboration of multidisciplinary team.

Friday, June 23, 2023

Session V – Hematology

HEMOGLOBIN S POLYMERIZATION AND RBC SICKLING EVALUATION IN SICKLE CELL

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Background: Sickle cell disease (SCD) is a life–threatening hematological disorder and the world's most prevalent hereditary disease. Anemia, vaso-occlusive and pain crises, infections, and a high rate of long-term comorbidities are hallmarks of this disease. The pathophysiology of SCD is due to a single point mutation (Glu6Val) that causes polymerization of the hemoglobin S and erythrocytes sickling. This change impairs RBC deformability and causes premature destruction of the RBCs. The standard of care includes symptomatic treatment, blood transfusions, Hydroxycarbamide and new drugs, and bone marrow transplant as curative therapy. Despite the tremendous progress in SCD care, novel methods are required to study the effects of drugs on SC-RBC and thus optimize individual patients' responses to treatment.
Aims & Methods: Study Aims: 1. Investigate the SC-RBCs sickling process and hydration status and evaluate SC-RBCs response to anti-sickling drugs.
2. Find a practical method for the evaluation of RBCs hydration and sickling process.
We set up a feasible high-throughput small sample method using flow cytometry (FC) for studying RBCs sickling in parallel to the light microscopy (LM) sickling, RBCs Percoll gradient separation, and membrane permeability studies.
Furthermore, we studied SC-RBC characteristics treated in vivo and or in-vitro with different dosages of Memantine a possible anti-sickling drug.
Blood samples were obtained from SCD patients treated at the Pediatric Hematology Unit, Emek Medical Center (EMC). The study was approved by EMC-IRB.
Results: We examined blood samples from 7 SCD patients for FC and LM sickling. 4 of the samples were studied before and after incubation with 100µM of Memantine for FC and metabolic examination. Different Memantine concentrations and incubation times were examined by LM.
Our results showed a time-scale response of sickling RBC both by LM morphology and FC with an increase in the Side scatter (SSC) and in the Forward scatter (FSC) parameters, (9.2% and 2.5% respectively). In addition, Memantine treated RBCs showed a reduction in sickling by LM and a trend of reduction in SSC and FSC. Percoll separation gradient revealed changes in RBCs layer distribution after sickling; with a protective effect after Memantine incubation. Metabolic examination showed an increase in membrane permeability of K+ after RBC sickling.
Conclusions: We found a high correlation between the flow cytometry sickling test and the classical light microscopy sickle cell detection. FC method may simplify and facilitate the evaluation of RBCs sickling, and patient's response to treatment; also, can be used for in vitro evaluation of anti-sickling

drugs. In addition, an in vitro anti-sickle cell effect of Memantine was observed, appearing as a possible useful therapeutic option in SCD; further studies are needed to confirm these results.

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FLOW CYTOMETRIC OSMOTIC FRAGILITY TEST FOR HEMOGLOBINOPATHIES CARRIERS SCREENING

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Background: The osmotic fragility test (OFT) is used to measure erythrocyte resistance to hemolysis while being exposed to varying levels of dilution of a saline solution. The hemodiluted or hypotonic solution, makes the cells swell and burst and is used to evaluate the stability of the erythrocyte membrane to osmotic stress and to confirm red blood cell disorders such as Hereditary Spherocytosis (HS). More recently, the flow-cytometric osmotic fragility test (FOFT) is being used to diagnose HS and other RBCs membrane disorders, with advantages in sample size, accuracy, and feasibility. Hemoglobinopathies are severe chronic diseases while the carriers are typically asymptomatic, the detection of carrier states is crucial for preventing the disease.

Aims & Methods: In this study investigates FOFT as a diagnostic tool for the carrier hemoglobinopathies state. We evaluated the pattern of each hematology condition. Including heterozygous for Sickle Cell (SC-Het), β Thalassemia (βT-Het), and for α Thalassemia (αT-Het), in comparison with healthy controls (HC) and iron deficiency (ID) conditions. Carriers were genetically and or HPLC diagnosed.

Flow-cytometric osmotic fragility method: Blood samples were exposed to 10 increasingly dilute solutions and the percent of RBCs per each dilution was calculated. FOFT was validated by comparison with the OF method measuring hemolytic activity by ELISA.

In addition, each sample was examined for complete blood cell (CBC) parameters, light microscopy, and RBCs Percoll gradient separation.

Iron deficiency was defined as Ferritin less than 15 ng/mL (normal hemoglobin and hemoglobin electrophoresis) Blood samples evaluated at Emek Medical Center (EMC) Clinical Hematology Laboratory were used for the study, after EMC-IRB approval.

Results: We examined a total of 50 individuals (~10 samples from each group).

CBC and light microscopy results, reveal as expected microcytosis and hypochromia together with abnormally low MCV and MCH values in βT-Het, αT-Het, and ID while SC-Het and HC were within normal values. Percoll gradient separation showed significant differences between the conditions in the upper fractions ($p=0.0104$) which indicate differences in younger and hydrated cells, showing also a specific pattern for αT-Het. A strong correlation was found between FOFT and OFT measured by ELISA (r Pearson =0.9856) validating this method in the studied population.

Significant differences were observed between the groups by FOFT with 45%, 40%, and 35% dilutions ($p<0.0001$), significant differences between βT-Het, αT-Het, and ID vs. healthy; βT-Het vs αT-Het was found; with no statistical difference found between αT-Het vs ID.

Conclusions: Flow-cytometric osmotic fragility together with RBCs separation gradient pattern and routine methods (CBC parameters, ferritin, and hemoglobin electrophoresis) give a great value in diagnosing hemoglobinopathies carriers; allowing the differentiation of the common microcytic

anemias α, β thalassemia carriers and iron deficiency. The advantage of these methods is that they are inexpensive, readily available and need a small sample size. More studies are required to support these findings and to evaluate combinations and different severity of the evaluated conditions.

Friday, June 23, 2023

Session VI - BMT

HAPLOIDENTICAL STEM-CELL TRANSPLANTATION FOR CHILDREN WITH ACUTE LEUKEMIA AND NON-MALIGNANT DISORDERS, USING AB+ T CELL /CD19+ B-CELL DEPLETION, A SINGLE CENTER EXPERIENCE

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Background: αβ+ T cells/CD19+ B cells depleted haploidentical Hematopoietic stem cell transplantation (αβ+ TCR/ CD19+ depleted haplo-HSCT) is increasingly used in children with acute leukemia (AL) and many non-malignant disorders (NMD) such as severe combined immune deficiency (SCID), inborn errors of immunity (IEI), bone marrow failure (BMF, acquired/congenital) and familial Hemophagocytic lymphohistiocytosis (HLH), in need of a transplant and not having a matched related donor. Within this heterogenous group of patients, it is important to try to define introductory requirements for successful outcomes, and to identify risk factors for transplant related complications.
Methods: Data was collected retrospectively regarding children age <21 years with AL or NMD who underwent αβ+ TCR/ CD19+ depleted haplo-HSCT at Sheba Medical Center between the years 2012-2021.
Results: Seventy-four children underwent αβ+ TCR/ CD19+ depleted haplo-HSCT, for AL and NMD.

Acute Leukemia subgroup:
Thirty-eight children had AL of them 35 patients (92%) engrafted successfully. The median time for neutrophil and platelet engraftment was 10 (range 9-17) and 13 (range 10-22) days, respectively. All children conditioned with either total body irradiation or treosulfan, fludarabine and thiotepa engrafted successfully. We observed 5-years overall survival (OS) and event free survival of 51% and 42%, respectively for the whole cohort. There were no cases of grade 3-4 acute graft versus host disease and only two patients had chronic graft versus host disease. EFS was higher in patients with graft composition of γδ+ T cells greater than the median value (MV) of 9.5X10^6 cells/kg than in patients who recieved cell dose lower than MV (54% vs 26%, P=0.04).

Non-malignant Disorders:
Thirty-six children had NMD. Twenty-six of them (72%) engrafted and ten had primary graft loss (did not achieved neutrophil count above 500 cells/uL at day 30). Engraftment kinetics was similar to AL subgroup. Secondary rejection was observed in two patients.
Conditioning regimen varied within this subgroup. For patients with BMF, busulfan or treosulfan/fludarabine was administrated. All patients with HLH conditioned with treosulfan/fludarabine/thiotepa regimen. Patients with SCID, either did not recieved conditioning or recieved fludarabine/thiotepa/melphalan or treosulfan/fludarabin conditioning. For patients with IEI

the protocol was based on treosulfan/fludarabin/thiotepa. Full donor chimerism was observed at day 30 in all patients who engrafted. Five-year OS was 56% for the whole cohort. OS was higher for patients without active infection at the day of transplant compared to patients with active infection (91.7% vs 33%, respectively, p=6.4X10-4). Mortality was high with thirteen patients dying from infection and one from veno-occlusive disease. Cumulative incidence of aGVHD was 30% and the majority were no greater than grade 2 and for cGVHD was 19%.

Conclusions: αβ+/CD19+ haploidentical Hematopoietic stem cell transplantation can offer long-term survival for children with acute leukemia and NMD.

For children with AL, we observed a presumed protective role for higher content of γδ+ T cell in the graft which need to be evaluate prospectively in a larger cohort. There were no cases of severe GVHD and the rate of grade 1-2 GVHD was low.

For children with NMD αβ+ TCR/CD19+ depleted haplo-HSCT is feasible and effective. Children with active infections at day 0 had poorer outcomes whereas children without an active infection had excellent outcomes. Thus, patients who have a clear indication for transplant should be evaluated for transplant as early as possible.

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MESENCHYMAL STEM CELL COUPLED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION IN RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB)

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Introduction: RDEB is autosomal recessive disease resulting from defective type VII collagen (C7), the main component of anchoring fibrils. Anchoring fibrils are needed to maintain the integrity of the cutaneous and mucosal basement membrane. In their absence, skin blistering occurs as a result of separation of dermis from epidermis. RDEB manifests with skin fragility with cycles of blistering and scarring, acute and chronic pain, pruritus, and progressive functional incapacitation. Complications include squamous cell carcinoma and amyloidosis. Recently, combined reduced intensity conditioning (RIC), bone marrow (BM) hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell (MSC) transplantation have been reported to attenuate the disease manifestations. We are presenting herein our experience with HSCT and MSC in RDEB.

Patients and methods: Between 2017 and 2019, 2 patients underwent RIC including cyclophosphamide 50mg/kg, fludarabine 6.4 mg/kg, ATG (horse) 90 mg/kg, and TBI 300 cGy. GVHD prophylaxis included cyclosporine and MMF. Both engrafted, improved clinically and remained alive with mixed chimerism. Between 2020 – 2021, 2 patients underwent RIC conditioning including cyclophosphamide 50mg/kg, fludarabine 6.4 mg/kg, ATG (horse) 90 mg/kg, TBI 400 cGy and post-transplant cyclophosphamide on days +3 and +4. Donor-derived MSCs were given on days +60, +100, and +180. Both patients engrafted and improved clinically. One remained alive with mixed chimerism, and improved skin manifestation and one rejected the graft.

Conclusions: RDEB is a devastating disease with life-long complications and limited life expectancy. Lately the introduction of MSC-augmented BM-HSCT has been found to improve outcome and quality of life in RDEB.

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TCRα/β+ DEPLETION USING CLINIMACS PRODIGY VS. CLINIMACS PLUS SYSTEMS: A HEAD TO HEAD COMPARISON

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Background: Depletion of TCRα/β+ T (and B) cells using the CliniMACS Plus (CP) has been used for a decade as an ex-vivo graft manipulation method for haploidentical hematopoietic stem cell transplantation (HSCT). Despite excellent clinical results, use of the procedure has been limited as it requires a highly trained staff, is time consuming, and its efficiency is user dependent. An automated platform, using the CliniMACS Prodigy device launched few years ago, overcomes these obstacles, but data regarding its efficiency and clinical outcome is scarce. Here, we report the first head to head comparison between the two methods including clinical outcome.
Results: We performed 18 procedures for 17 patients using CP between 2015-2021, and 8 procedures for 8 patients using Prodigy between 2021-2022, Results are shown in table 1. No significant difference was found in CD34 % recovery, though when comparing to starting material, the CD34% recovery is close to reach a statistical significance (with better recovery using the Prodidy), suggesting more cell loss in the pre-separation stages using the CP. The TCRαβ log depletion was significantly higher using Prodigy, reflecting a better efficacy and resulted in less patients requiring additional GVHD prophylaxis.
Analyzing clinical parameters, engraftment was more rapid with Prodigy-processed grafts, though no difference was found in terms of engraftment rates or acute rejection which were mainly influenced by the patient's primary disease. Acute GVHD was limited to grade 1 skin GVHD in both groups. Relapse rates were significantly higher after CP-processed grafts, but many of the patients in this cohort were undergoing second transplants.
Conclusion: We found TCRαβ depletion using the CliniMACS Prodigy more efficient than procedures using CliniMACS Plus, with comparable clinical outcome. The elimination of operator-related variables produces a reliable product with a substantial reduction of work-load for the laboratory staff.

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SYSTEMIC EFFECTS OF ORAL BUDESONIDE GIVEN FOR GASTROINTESTINAL-GRAFT VERSUS HOST DISEASE TREATMENT, IN CHILDREN AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATIONS

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Introduction: Graft versus host disease (GVHD) is a major complication in patients following allogeneic hematopoietic stem cell transplantation (HSCT), and systemic glucocorticoids are the first-line treatment. Topical steroids such as oral Budesonide can be given for gastrointestinal (GI) GVHD, either with or without systemic glucocorticoids. Data on the systemic effects of topical glucocorticoids, when given *without* concurrent systemic steroids, in pediatric patients, is partial, particularly regarding their impact on adrenal function. Recent literature points to the increased effect of Budesonide when combined with anti-fungal medications.

Aim: In this study we aimed to identify the occurrence of systemic effects of oral Budesonide (*without* concurrent systemic steroids), in pediatric patients with acute or chronic GI-GVHD, following allogeneic HSCT.

Methods: This is a retrospective chart review, which included all children and adolescents aged 0-20 years, treated with oral Budesonide for GI-GVHD, *without* concurrent systemic steroids, at the Pediatric Bone Marrow Transplants, Rambam medical center, between the years 2010-2021. Data was collected through Mdclone and by screening electronic medical charts. We searched for symptoms and signs of systemic effects of Budesonide including cushingoid features and laboratory data suggesting adrenal suppression, during the treatment.

Results: Twenty-seven patients met inclusion criteria. Twelve (44.4%) of them demonstrated systemic effects of glucocorticoid treatment: all 12 had low morning cortisol levels while treated with Budesonide, in 10 of 12 (83%) the level was undetectable (<27nmol/L), and 6 of 12 (50%) had cushingoid features. Interestingly, 7 of the 12 (58%) received concurrent antifungal treatment (either Fluconazole, Voriconazole, or Posaconazole).

Conclusions: Almost half of the patients demonstrated adrenal suppression while on Budesonide treatment *without* concurrent systemic steroids; Concomitant anti-fungal treatment was common. Our findings emphasize that although generally considered to have mostly local GI therapeutic effects, surveillance for the systemic effects of oral Budesonide is important.

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Posters

OMPARISON BETWEEN PERIPHERAL AND CENTRAL BLOOD CULTURES IN PEDIATRIC ONCOLOGY PATIENTS WITH BLOODSTREAM INFECTIONS

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Background: Current guidelines for fever in children with cancer recommend obtaining blood cultures from all lumens of central venous catheter (CVC) and to consider a concurrent peripheral blood culture. We assessed the characteristics of blood stream infections (BSI) in oncology pediatric patients and compaered central and peripheral pathogen growth.
Methods: An ongoing, prospective, computerized surveillance of BSI in children and young adults treated at the oncology unit between May 2014- July 2020. The growth of the same organism within a month was considered a single episode, ≥2 organisms in the same culture were defined as different episodes. Only children with concomitant cultures, drawn at presentation prior to initiation of antibiotics were included in the comparison between CVC and peripheral cultures.
Results: 139 episodes in 81 children (all with implanted Port-A-catheters) were considered true BSI. CVC and peripheral cultures were concomitantly obtained in 94/139 (67.6%). In 31/94 (33.0%) a pathogen grew only from CVC, in 11/94 (11.7%) the pathogen grew only from peripheral. In 52/94 (55.3%) both cultures were positive, 4/52 (7.7%) of the isolates having the same identification had different susceptibility testing results. Significantly higher CVC removal rates were observed when both peripheral and CVC cultures were positive (P-0.044).
Conclusions: 11.7% of true BSI episodes in oncology children were identified only by peripheral culture and 7.7% of paired organisms did not share the same susceptibility test results which emphasize the importance of a peripheral culture in managing fever in oncology children.

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THE ROLE OF HYDROXYCHLOROQUINE IN THE MANAGEMENT OF CHILDREN WITH ITP AND POSITIVE ANTINUCLEAR ANTIBODIES

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Introduction: Pediatric Immune thrombocytopenia (ITP) is usually primary often induced by a viral infection. Yet ITP may also be secondary to autoimmune disorders. Adolescents with ITP are routinely screened for systemic lupus erythematosus (SLE) with antinuclear antibody (ANA) titer. If positive, additional testing for SLE is warranted. Hydroxychloroquine (HCQ) is a safe, effective immunomodulatory drug used in the treatment of SLE and is also used rarely in secondary ITP in adults with some long-term responses.

Aim: We analyzed the efficacy and safety of HCQ in treatment of pediatric ITP patients with positive ANA.

Methods: A retrospective, single center study, including all children with ITP who repeatedly tested positive for ANA (>1:80), and were treated with HCQ, between 2010-2021. Inclusion criteria were children fulfilling accepted diagnostic criteria of SLE or with incomplete SLE score who required immunomodulatory therapy with HCQ. The platelet response to HCQ was documented at several time points. "Complete response" (CR) defined as platelet count of at least 100 *10 9 /L and "Response" (R), platelet count between 30-100 * 10 9/L and at least doubling of the baseline count.

Results: 16 patients (14 female) were included, 12 with definite SLE and four with incomplete SLE, median age was 15 years (10-17.3) HCQ was started at median of 5.5 months (0-120) post ITP diagnosis, mean platelet count at initiation was 41.8+20.3*109/L (with 13/16 on ITP therapy). At 8 weeks 7/16 (43%) responded, 5 achieved CR. At one-year, overall response was 81.2% (13/16), the remaining patients had stable platelet counts, needing no additional ITP therapy. The response was significant and maintained at a median follow-up of 42 months (range 6-120). No adverse effects to HCQ were documented.

Conclusion: Pediatric ITP patients with positive ANA who fulfill, fully or partially, criteria for SLE may benefit from early initiation of HCQ.

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FULMINANT LIVER AND RENAL FAILURE IN A CHILD WITH SICKLE CELL DISEASE ON DEFERASIROX

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Deferasirox (Exjade) is an oral iron chelator used to treat chronic iron overload caused by various hematological diseases and chronic blood transfusions. Its main side effects include gastrointestinal complaints and rash. Additionally, there is substantial literature documenting deferasirox induced renal injury, including Fanconi syndrome. There is less documentation of hepatic injury and very few reports of fulminant hepatic failure associated with deferasirox treatment. Here we describe a case of a seven-year-old girl with sickle cell disease, who developed acute renal failure requiring dialysis and fulminant hepatic failure, occurring shortly after reconstitution of deferasirox therapy. Though rare, these are severe life threatening complications of deferasirox treatment, that merit consideration and acknowledgement by hematologists, nephrologists, hepatologists and intensive care specialists alike. We will present a case and a review of the literature.

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LOW-LEVEL LASER THERAPY (LLLT) FOR PEDIATRIC ORAL MUCOSITIS INDUCED BY CHEMOTHERAPY

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Laser therapy for the treatment and prevention of chemotherapy induced oral mucositis was first recommended for adults in 2014 by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO).
Since then many centers have adopted this treatment method although randomized studies proving its efficacy are scarce and focused mainly on adult patient population.
We herein report the results of 13 patients treated at the pediatric hemato-oncology department of the Hadassah Medical Center in 2022. These patients were treated with oral low-level laser therapy (LLLT) – also known as photobiomodulation.
All patients were younger than 22, and 10 were aged 18 and younger. They were treated with different chemotherapy protocols and suffered from oral mucositis which was treated with standard treatments including analgesia and oral hygiene protocols. Since these treatments were not efficacious enough and patients were unble to eat or drink, they received at least one session of LLLT. All of them responded well and their ability to drink and eat improved. The effect of this treatment lasted at least couple of hours, and in few the dose of analgesic treatment could be reduced. No adverse events were reported with this treatment.
In conclusion LLLT has been shown to benefit 100% of the patients treated in our department. These results support the conduction of large randomized trials with this treatment modality for children suffering from oral mucositis induced by chemotherapy, to determine its clear role in the treatment paradigm.

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DOES WEIGHT LOSS IMPAIR RESPONSE TO CHEMOTHERAPY IN PEDIATRIC PATIENTS WITH OSTEOSARCOMA?

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Aims: To evaluate the correlation between weight loss and response to chemotherapy in pediatric patients with osteosarcoma
Methods: All medical files of patients treated for osteosarcoma in a single pediatric haemato-oncology center between January 2011 and October 2022 were retrospectively reviewed.
Results: Sixty-three patients were included. The change in body weight between the initiation of neo-adjuvant chemotherapy and local therapy (tumor resection) was evaluated. Response to chemotherapy was evaluated using the percentage of tumor necrosis at the time of surgery. There was a statistically significant direct correlation between weight loss and good response to chemotherapy as demonstrated by tumor necrosis above 90%.
Conclusion: Low caloric intake may resemble caloric restriction diet that was proven to improve response to therapy in some oncologic diseases. Further prospective trials are needed for the establishment of recommended caloric intake during chemotherapy in patients with osteosarcoma.

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INCIDENCE OF BEVACIZUMAB ASSOCIATED TOXICITY IN CHILDREN WITH LOW GRADE GLIOMA WITH AND WITHOUT NF1

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Background: Low grade gliomas (LGG), both sporadic & Neurofibromatosis1 (NF1) associated, are the commonest pediatric brain tumors. When surgically unresectable, they may become progressive/ symptomatic and require chronic oncological treatment. Bevacizumab (BVZ; Avastin), a recombinant humanized monoclonal antibody to VEGF, has shown efficacy both as a single agent or combined with chemotherapy as second/ third line treatment of progressive LGG especially in the optic pathway. BVZ can be associated with adverse effects including hypertension (HTN) and proteinuria. Children with NF1 have known increased tendency to hypertension however there is no data comparing the frequency of side effects from BVZ in patients with or without NF1.
Aim: To compare the incidence of BVZ associated toxicity in children with LGG with and without NF1.
Methods: Retrospective study of all LGG cases treated with BVZ diagnosed 2010-2023 in a tertiary oncology center.
Results: 16 children with LGG were treated with BVZ; 7 had NF1. 75% optic glioma, 25% other. All received BVZ as second or third line treatment in combination with chemotherapy. In the non NF1 group, 77% patients developed grade 2 HTN on BVZ treatment; none required medical intervention. 6 had grade 1 elevation of protein-creatinine ratio (median 0.38). In the NF1 group, 71% developed grade 2 or 3 HTN on BVZ treatment including a patient with aortic coarctation (CoA) who had worsening of previous HTN, 2 required antihypertensive therapy (p non-significant HTN non NF1 vs. NF1). Only 1 NF1 patient developed proteinuria. No patients in either group stopped BVZ prematurely for toxicity. Hypertension was reversible after cessation of BVZ in all except the patient with CoA.
Conclusions: Hypertension is more common than previously reported in both NF1 and non-NF1 patients treated with BVZ for LGG. Blood pressure should be monitored and treated appropriately. BVZ is safe in young patients with NF1.

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THE DELINEATION, PREVENTION AND TREATMENT OF REWARMING DEATHS IN HYPOTHERMIA CAUSED BY (DRT) DELAYED REWARMING THROMBOCYTOPENIA

Ian Cohen[1,2]

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While researching thrombocytopenia in neonates suffering from neonatal cold injury we had the good luck of performing, by mistake, an aggregation study at room temperature, the aggregation seen was much greater than that seen at body temperature. We were able to show that it was reversable on rewarming, and resulted from the absence, we found, of the second stage of aggregation below 32^0C. This "first stage platelet hyper-aggregation" explains the reversible sequestration seen in the liver and spleen in hypothermic mammals, the same platelets reappearing in the circulation on rewarming. Using increasing amounts of ADP to cause aggregation did not result in a second wave of aggregation at any concentration of ADP. Rewarming platelets during these experiments showed that following the use of a critical concentration of ADP (much lower than that required at body temperature) instead of de-aggregation, an augmented irreversible second stage of aggregation occurred "second stage platelet hyper-aggregation". Luciferase aggregometer studies showed an associated ADP release reaction. Aspirin given before rewarming, blocked the second stage aggregation. During prolonged hypothermia, APD is released from erythrocytes and is a potential cause of the second phase of aggregation. This results, in vivo, after a 24 hours "hypothermia duration" as a potentially fatal thrombocytopenia. In our small series of neonates, who were followed with platelet counts during rewarming, platelets (that are incidentally stored without erythrocytes) were curative. No consensus of prognostic factors exists for hypothermia suggesting that at least one additional prognostic factor exists. The published data of hypothermia supports platelet pathophysiology as being the critical unrecognized prognostic factor in hypothermia. The significance of thrombocytopenia in hypothermia seems to have been overlooked because of the well-known occurrence of reversible aggregation and any subsequent severe thrombocytopenia was assumed to be due to DIC rather than DRT (Delayed Rewarming Thrombocytopenia).

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18F-FDG-PET/CT IN THE ASSESSMENT OF BONE MARROW INVOLVEMENT IN PEDIATRIC NON-HODGKIN LYMPHOMA- A SINGLE CENTER EXPEREIENCE

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Background: The role of 18F-FDG-PET/CT in pediatric Hodgkin lymphoma is well established and has replaced bone marrow biopsy (BMB) for the assessment of bone marrow involvement (BMI). Data regarding the utility of PET/CT for detecting BMI in pediatric non-Hodgkin lymphoma (NHL) is scant.
Objectives: To evaluate the role of 18F-FDG-PET/CT scan in the detection of BMI in pediatric NHL patients; its sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) compared to those of BMB.
Methods: All pediatric NHL patients treated in our department from 6/2009-02/2023 who had undergone both diagnostic PET/CT and bilateral BMB from the posterior superior iliac crests were included in the analysis. Scans were interpreted by a senior nuclear medicine physician blinded to the BMB results. Patterns of bone marrow 18F-FDG uptake and localization were compared with pathology results of BMB.
Results: 44 patients were included, 32 boys and 12 girls; median age 9.5y (range 1.6-16.2y). 20 patients had Burkitt lymphoma (BL), 9 diffuse large B cell lymphoma (DLBCL), 10 lymphoblastic lymphoma (LL), 4 anaplastic large cell lymphoma (ALCL) and 1 follicular lymphoma. 32/44 patients had no BMI according to BMB and PET/CT imaging. Five of them demonstrated reactive bone marrow FDG uptake, all had negative BMB. The remaining 12/44 patients (3 DLBCL, 4 BL, 4 LL, 1 ALCL) had positive findings on PET/CT with multi-focal BM uptake compatible with BMI. Out of those 12 patients, 6 had negative BMB (3 DLBCL, 2 BL, 1LL) and 6 had positive BMB (2 with BL, 3 with LL, 1 with ALCL). No patient had a positive BMB with negative BM uptake on PET/CT. According to our results, 12/44 (27%) patients had BMI according to PET/CT while only 6/44 (13%) had BMI according to BMB. This relates to a sensitivity, specificity, PPV and NPV of 100% each for PET/CT compared to 50%, 100%, 100%, and 84% for BMB respectively.
Conclusions: PET/CT had a high level of accuracy in the evaluation of BMI in our cohort of 44 patients. BMB failed to demonstrate involvement in 50% of patients that had positive multifocal uptake on 18F-FDG- PET/CT scan. The sensitivity of the BMB was probably compromised by the focal pattern of BMI and the blinded selection of the BMB site at the posterior superior iliac crest.