HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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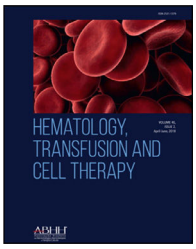

PEDIATRIC PRESENTATIONS

Sp01

TREATMENT OF SICKLE CELL ANEMIA

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Sickle cell disease (SCD) is an inherited disorder prevalent in many areas of the world including Africa, Middle East and parts of India. It is characterized by repetitive episodes of vaso-occlusive (VOC) process, leading to recurrent painful episodes, hemolytic anemia and predisposition to infection. Although VOC is a leading manifestation of SCD, and seen in about 90% of all patients with SCD, however organ specific complications such as acute chest syndrome, stroke, splenic sequestration, and many skeletal complications are also seen. Better understanding of pathophysiology of the disease as well as worldwide interest in the disease has allowed more progress on treatment and prevention of these complications and development of more focused pharmacological therapies. Hemoglobin polymerization is a primary triggering event in the pathophysiology of the disease, resulting in vascular injury and leading to the process of sickling. This usually ignite an intense inflammatory process/ tissue ischemia and increased adhesions. This understanding of the pathophysiology has allowed scientist to develop drugs (three FDA approved within the last few years), that interfere with these processes such as Voxelotor & Hydroxyurea (interfere with polymerization and enhance HbF production), L-glutamine and Omega 3 (interfere with inflammatory process and oxidative stress) and Crizanluzimab and Tinzaparin (works by inhibiting adhesion molecules). Others studies looking at similar and other pathways are ongoing, including drugs that improve adenosine triphosphate (ATP) levels and reducing 2,3-diphosphoglycerate (2,3-DPG) levels. The availability of these therapeutic interventions, will allow patients and physicians the freedom to have patient specific therapeutic interventions including development of combinations protocols. SCD is very complex and this meant that drug with multi-faceted action such as Hydroxyurea will remain with us for some time. Further progress also made in the area of bone marrow transplant (including alternative donor pool) and gene therapy /gene editing, with recently published data is very encouraging. Although the prognosis of patients with SCD has improved, due to introduction of vaccination, use of antibiotics prophylaxis and blood transfusions, however still patients are dying prematurely and further work is needed on understanding disease and its manifestation.

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Sp02

EARLY T-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDHOOD

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Early T-cell precursor (ETP) ALL accounts for 10% to 15% of T-ALL, which arises from an early T-cell lineage clone with aberrant expression of myeloid and/or early progenitor cell markers (1,2). ETPs are a subset of thymocytes representing recent immigrants from the bone marrow to the thymus, they retain multilineage differentiation potential, suggesting their direct derivation from hematopoietic stem cells (3). ETP-ALL, which was first reported by Coustan-Smith in 2009, largely overlaps with the pro-T subtype of the EGIL classification; its special diagnostic criteria in immunophenotypic screening are the absence of CD1a and CD8 expression, the absence or weak expression of CD5, and the presence of strong positive for at least one of CD34, CD117, HLADR, CD13, CD33, CD11b, and CD65 (2,4-6). In case of strong positivity of CD5, at least two of the latter must be strong positive (6). There is also novel evidence that the myeloid marker CD371 may be positive in ETP (6). The genetic features of ETP-ALL are similar to those of hematopoietic stem cells and myeloid progenitor cells. The genomic mutations of ETP-ALL are enriched in hematopoietic transcriptional regulators (such as BCL11B, ETV6, RUNX1, biallelic WT1, and GATA3), epigenetic factors

(such as histone modification, including PHF6, CTCF, EED, EZH2, SUZ12, and SETD2), and signaling genes (such as activation JAK-STAT, IL-7R and RAS signaling pathway, including JAK1, JAK3, IL7R, SH2B3, NRAS, KRAS, FLT3, NF1, and PTPN11). ETP-ALL has a lower frequency of classical T-ALL genetic alterations such as NOTCH1/FBXW7/CDKN2A mutations and a higher prevalence of FLT3, NRAS/KRAS, DNMT3A, IDH1, IDH2, JAK3, and ETV6 mutations (1,2,5). ETP-ALL was initially thought to have a poor prognosis, but the opinions on it vary (2,3,7). ETP ALL is often corticosteroid resistant and a high percentage of ETP ALL patients have detectable MRD at day 29 including many induction failures (1,2,7,8). No difference in OS was observed in the COG AALL0434 study and UKALL 2003 trial between the patients with ETP-ALL and typical T-ALL (4,9). Therefore, it is important to continue with conventional therapy in ETP-ALL patients who have poor end-induction response; MRD based therapeutic approach is recommanded (7,10). Patients with ETP-ALL had high risk of hematological relapse treated at St Jude Children's Research Hospital (3). For relapsed and refractory patients, the use of acute myeloid leukemia-oriented therapies such as FLAG-IDA regimen or targeted agents may be of benefit for some patients, including FLT3 inhibitors, tyrosine kinase inhibitors, BCL-2 inhibitors such as venetoclax, or JAK/STAT inhibitors in patients with JAK mutations or fusions (1,2,4,5,7).

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Sp03

SUBCUTANEOUS TREATMENT MODALITIES IN HEMOPHILIA CARE IN 2022

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Hemophilia is a rare hereditary, recessive X-linked, hemorrhagic disorder characterized by deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B). A typical presentation of this disease is spontaneous or traumatic bleeding. Although bleeding can occur in any part of the body, the most frequently affected parts are the joints and muscles. Bleeding into the joints (hemarthrosis) can lead to stiffness, pain, swelling and severe joint damage which can cause the patient severe long-term disability and potentially death if untreated. A while ago, **prophylaxis** with **factor concentrates** started at an early age in children with severe or moderate hemophilia, has proven its efficacy over **on demand treatment** in minimizing the hemorrhagic risk and so the long-term sequelae. Subsequently, after the introduction of **extended half-life** factor concentrates, patients are living longer and ''better'' as a result of safer factor concentrates, and less treatment burden on young patients. Despite the great efforts of clinical research, until recently there were no treatments other than replacement factors. Lately, **"non-factor therapies"** gained their place in the treatment armamentarium of hemophilia. Those are medications that improve hemostasis without replacing the missing factor. These therapies are all designed to be given **subcutaneously** and at relatively **infrequent intervals** and thus reducing the treatment burden. The aim of our presentation is to shed the light on different families of "non-factor therapies": **bispecific monoclonal antibody** like **emicizumab** (approved and available to clinicians for the subcutaneous treatment of hemophilia A) and **MIM8** (under investigation), **rebalancing agents** like **fitusiran (an antithrombin inhibitor)** and the **anti-TFPI** (Tissue Factor Pathway Inhibitor) antibodies, as **marstacimab or concizumab**.

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Sp04

STEM CELL TRANSPLANTATION IN BRAIN TUMORS

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Central nervous system (CNS) tumors are the second most common pediatric malignancies after acute leukemias and are the most common pediatric solid tumors. Although cure rates have improved with numerous technical advances in multimodal therapy, the prognosis remains poor for some high-risk histological type and for patients with residual, recurrent or disseminated disease. Radiotherapy (RT) remains an integral part of treatment for childhood brain tumors; however, the profound and irreversible sequelae of brain irradiation in the younger children are now well documented. In an effort to decrease irradiation toxicity while improving survival and quality of life in these patients, high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HD-CT&autoHSCT) has been incorporated in both up-front as well as recurrent therapies. In up-front treatment, it is used in patients under the age of 3 years to delay RT or not to use RT at all. It can be used tandem non-myeloablatively in patients older than 3 years of age, after dose-intensive chemotherapy, both to shorten the neutropenic period and to give more intense chemotherapy in a shorter time when compared to conventional chemotherapy treatment approaches. AutoHSCT may also be considered after a myeloablative conditioning regimen for relapsed embryonal brain tumors, as either once or tandem, in cases with good response to salvage therapy as consolidation. In this talk, the role of autoHSCT in childhood brain tumors will be discussed by giving the results from international studies.

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Sp05

TREATMENT/MANAGEMENT OF OTHER HEPATIC TUMORS

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