HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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PEDIATRIC PRESENTATIONS

Sp01

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH CENTRAL NERVOUS SYSTEM TUMORS

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Central nervous system (CNS) tumors are still the most common malignant solid tumors in childhood and constitute 16-25% of all tumors (1). Most tumor types include malignant gliomas, ependymoma,medulloblastoma, and atypical teratoid rhabdoid tumors (2). Surgery, radiotherapy (RT), and chemotherapy are the primary treatment modalities, and the prognosis in some histopathological subtypes and recurrent or residual diseases is, unfortunately, still poor. In cases under three, avoiding radiotherapy due to the long-term side effects adversely affects the prognosis. For this reason, the studies on high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HDC/AuHSCT) are mostly conducted on recurrent CNS tumors, cases under three years old, and medulloblastoma which is a chemosensitive tumor.

The most crucial factor in increasing the success of the transplant is minimizing the tumor burden before transplantation. The minimal residual disease generally includes residual tumor <1.5 cm2, no tumor cells in cerebrospinal fluid, and minimal radiological signs in metastatic sites (3). Chemotherapeutics with good CNS penetration should be selected in the conditioning regimen. Carmustine, thiotepa, and melphalan are some of these drugs (4).

Considering the low number of patients with malignant gliomas, the 4-year overall survival (OS) rates range from 30-46% (5,6), while the 2-year OS rates were found to be 46% in the study of the Children Cancer Group with 86 cases. The study was terminated early due to pulmonary toxicity (7). In pontine gliomas and ependymomas, the effect of transplantation on treatment success has not been demonstrated (8-11). In a meta-analysis evaluating patients with metastatic atypical teratoid rhabdoid tumors, HDC/AuHSCT was shown to improve survival ($p<0.0001$) and reduce the risk of mortality ($p<0.0001$) (12). The study of the European Rhabdoid Registry has shown that selected cases may benefit from transplantation together with RT (13). In the study performed by the St. Jude group on newly diagnosed medulloblastoma cases, 5-year event-free survival (EFS) was found to be 83% and 70% in the high-risk and average-risk groups (14). In the Head Start III study, RT was not applied to the patients who were younger than six years of age and had nonmetastatic tumors at diagnosis, and had no residual tumors after induction therapy, and HDC/AuHSCT was performed. The 3-year RT-free EFS was 49.5% in the whole group, and the 5-year EFS was 88% in the desmoplastic group (15). The Children Oncology Group's study applied tandem consolidation treatment with HDC/AuHSCT to 36 medulloblastoma cases. Five-year EFS was 60% in the entire group (16). These studies show that a high survival rate can be achieved without affecting neurocognitive functions.

In conclusion, HDC/AuHSCT is a treatment option that can be applied in some CNS tumors. Specifically, it can be applied when the patient is under three years of age, without affecting neurocognitive functions and reducing survival rates despite not performing RT.

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Sp 02

STEM CELL TRANSPLANTATION AS A TREATMENT OPTION FOR RELAPSED/ REFRACTORY GERM CELL TUMORS

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Malignant germ cell tumors (GT) arise from abnormal migration of primordial germ cells and are histologically identical whether they occur inside or outside of central nervous system (CNS) (1). They are divided into two heterogenous groups: germinomas and non-germinomatous germ cell tumors according to histological findings. Although the optimal treatment strategy remains a matter of debate, they generally respond well to surgery, radiotherapy, chemotherapy, or a

combination of all and are characterized by a good survival rate (2). The surgical strategy for GCTs varies depending on the location of the tumor. Surgery is only a standard care option for low grade extracranial GCTs because it is unlikely to achieve negative tumor margins when the tumor is located inside CNS (2). Patients with relapsed or progressive despite initial chemotherapy are candidates for salvage therapy (3). Patients relapsing after definite treatment of locoregional disease are to be treated by stage adopted first line standard therapy for metastatic disease. Patients with primary advanced/metastatic disease failing one line of cisplatin based combination chemotherapy can benefit from high dose chemotherapy and stem cell rescue (4). Although stem cell transplantation following high dose chemotherapy can be beneficial, either two or three consecutive cycles of high dose chemotherapy with repetition after blood count recovery may contribute to overall survival rates.

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Sp03

CURRENT THERAPIES PRIMARY LANGERHANS CELL HYSTIOCYTOSIS

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Langerhans cell histiocytosis (LCH) is a neoplastic histiocytic disorder that most commonly affects bones and skin, but it can also involve the bone marrow, liver, spleen, lungs, pituitary gland/central nervous system, and other organs. LCH is rare, but it is considerably more common in children (especially younger children) than in adults

LCH is so-named because the neoplastic cells resemble dendritic Langerhans cells in the skin and mucosa; however, the CD1a+, CD207+ neoplastic cells of LCH are derived from myeloid dendritic cells, rather than from epidermal Langerhans cells. The *BRAF* V600E mutation is present in more than half of cases, and activation of the mitogen-activated protein kinase (MAPK) pathway is a key driver of this neoplastic disorder.

According the Histiocytic Society classification, histiocytic disorders divide into five categories, based on clinical, histologic, immunophenotypic, and molecular features.

- Langerhans (L) group: The L group includes LCH, Erdheim-Chester disease (ECD), mixed LCH/ECD, indeterminate cell histiocytosis, and extracutaneous juvenile xanthogranuloma.
- Cutaneous and mucocutaneous (C) group
- Rosai-Dorfman disease (R) group
- Malignant histiocytosis (M) group
- Hemophagocytic lymphohistiocytosis (H) group

Symptoms, affected organ systems, and disease tempo of LCH vary between patients. Affected individuals range from neonates to adults, although it is more common in young children than adults. The diagnosis may not be made for years after the first clinical manifestations because of its variable presentation.

LCH can present as a single site or multiple sites of disease in one organ (eg, in bone or skin) or it can present in multiple organ systems simultaneously or sequentially. This distinction is important for determining prognosis and disease management

➢ **Single-system LCH** – Patients who present with single-system LCH can be of any age; they typically do not have systemic symptoms of weight loss or fever. The following organs are most often affected and can exhibit unifocal or multifocal involvement:

- Bone
- Skin
- Lungs
- Pituitary
- Central nervous system (CNS)
- Lymph nodes (excluding draining lymph node of another LCH lesion) and other rare locations (eg, thyroid, thymus)

➢ **Multisystem LCH** – Two or more organs/systems are involved. Among patients with multisystem disease, it is important to identify those with involvement of critical organs (CNS and lung) and "risk" organs (bone marrow, liver, spleen).

➢ **Children** – Among children, LCH is limited to one organ system in approximately 55 percent of cases; the remainder present with multisystem disease . Acute disseminated multisystem disease is most often seen in children <3 years, while involvement of a single organ is more common in older children and adults.

A report involving 1741 children with LCH registered in prospective trials reported the following areas of involvement at the time of diagnosis

- Bone – 77 %
- Skin – 39 %
- Lymph nodes – 19%
- Liver – 16%
- Spleen – 13%
- Oral mucosa – 13%
- Lung – 10%
- CNS – 6%

Adults most commonly present with skin rash, skull or jaw tumor, dyspnea or tachypnea, polydipsia/polyuria, bone pain, lymphadenopathy, weight loss, fever, gingival hypertrophy, ataxia, and memory problems

Management – Management of LCH is guided by the extent and severity of disease, as determined by the pretreatment evaluation.

- Single-system versus multisystem disease
- Involvement of central nervous system (CNS) or a critical ("risk") organ (bone marrow, liver, or spleen)
- Unifocal versus multifocal/extensive disease
- Symptoms
- Age – Preferred systemic treatment for children (≤20 years)

Single-system disease

- Bone-only –Single bone – Curettage provides tissue diagnosis and treatment. Radiation therapy (RT) may be used for selected adults, but not children.
- Multiple bones – For ≥2 bone lesions, lesion ≥5 cm, femoral or vertebral involvement, or CNS-risk bone (ie, orbit, mastoid, temporal, sphenoid), treatment involves systemic therapy.

Surgery or RT may be added in selected cases.

- Skin-only – Topical steroids or mustard, or oral hydroxyurea, methotrexate, thalidomide, or lenalidomide can be effective.
- Multisystem – Multisystem disease requires systemic therapy.
- Children – For initial systemic treatment of children with LCH, we suggest induction therapy with vinblastine plus prednisone (V-P), rather than other chemotherapy regimens or a targeted agent (Grade 2C).

Treatment response guides further management; continuation therapy is 12 months for response to V-P.

- CNS or risk organ involvement – For adults with BRAF V600E-mutated LCH and involvement of CNS or a risk organ, we suggest a BRAF inhibitor (eg, vemurafenib, dabrafenib), rather than systemic chemotherapy (Grade 2C).

For adults with BRAF wildtype LCH with CNS or risk organ involvement, we suggest cytarabine or cladribine, rather than combination chemotherapy or a targeted agent (Grade 2C).

- Response assessment – Positron emission tomography (PET) is preferred for response assessment, but computed tomography (CT), magnetic resonance imaging (MRI), or clinical assessment is used when PET is not available or appropriate (eg, brain lesions).
- **Long-term surveillance** – Patients are at risk for treatment-related toxicity, second cancers, and endocrine complications.

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Sp04

THROMBOSIS IN CHILDHOOD LEUKEMIA AND LYMPHOMA

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Thrombosis in childhood usually develops secondary to underlying causes. One of the most important risk factors is cancer. It has been reported that the incidence of thrombosis in children with cancer is 2-16% when symptomatic thrombosis is mentioned and it climbs up to 50% if asymptomatic conditions are included. Thrombosis associated with childhood cancers is multifactorial. In addition to the prothrombotic effect of cancer, mass effect, vascular invasion of cancer, drugs used (e.g., steroid, asparaginase), catheter, infection, immobilization, surgery, total parenteral nutrition, and comorbid genetic thrombophilia are the most important underlying etiologies. Thrombosis can cause morbidity, mortality, as well as inadequate or delayed treatment. Among childhood cancers, thrombosis risk is more common in acute lymphoblastic leukemia and lymphoma than in solid malignancies. Among the drugs used for the treatment of thrombosis, low molecular weight heparin constitutes the most important group. Warfarin, on the other hand, can be preferred in case of long-term use, but its use may be challenging due to polypharmacy and nutritional instability on warfarin efficiency. Thrombolytic therapies are rarely used in selected cases. In addition to general measures to reduce the risk of thrombosis, prophylaxis is controversial. Prophylaxis has not been included in the standard guidelines for the prevention of thromboembolic complications in childhood. It can be considered for use in high-risk patients. However, prophylaxis during cancer treatment may be more challenging, especially in this group of patients who need frequent interventions (e.g., intrathecal treatments) and have an increased risk of bleeding secondary to thrombocytopenia and coagulopathies. There are many continuing studies on the prophylactic and therapeutic use of new-generation anticoagulants in childhood.

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Sp05

CANCER TREATMENT-RELATED CARDIOTOXICITY: OPTIMIZING HEART HEALTH FROM DIAGNOSIS TO LONG-TERM FOLLOW-UP

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Improvements in overall survival rates for children diagnosed with cancer have led to a growing number of long-term childhood cancer survivors and an increasing recognition of the late health conditions they may experience. Among these are cardiac conditions, most commonly associated with prior anthracycline chemotherapy and chest-directed radiation exposing the heart. Potential late effects of anthracycline chemotherapy and chest-directed radiation therapy include cardiomyopathy, subclinical left ventricular dysfunction, heart failure, and arrhythmia. In addition, chest-directed radiation exposing cardiac substructures has been associated with risk for pericarditis, pericardial fibrosis, valvular disease, atherosclerotic heart disease and myocardial dysfunction. Patient (e.g., age at exposure, family history, genetic variation) and treatment (e.g., cumulative dose, multimodality cardiotoxic therapy) factors influence the magnitude of risk. In addition, co-morbid medical conditions (e.g., hypertension, diabetes, dyslipidemia, obesity) and health behaviors (e.g., smoking) can exacerbate risk in aging survivors. Recognition of treatment associations and adverse cardiac outcomes has informed risk-stratification strategies used in contemporary protocols and guided health surveillance recommendations for long-term survivors. Dexrazoxane has also been used for primary prevention of anthracycline cardiotoxicity in high

exposure groups. Screening guidelines recommend frequency-adapted (based on cumulative cardiotoxic exposures) echocardiography to facilitate early identification of cardiomyopathy as well as attention to modifiable cardiovascular disease risk factors and health behaviors. This presentation will provide an overview of cardiotoxic cancer treatment modalities and current approaches to prevent cardiac disease and preserve cardiac function.

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Sp06

TRANSFUSION IN PEDIATRIC ONCOLOGY

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Transfusion of blood components is a critical – life-saving - part of the care of children with hematologic and oncologic diseases. According to studies, pediatric oncology patients account for approximately 25% of all inpatient pediatric transfusions in clinical practice. Pediatric oncology patients may require multiple transfusions of blood components, including red cells, platelets, and plasma, due to underlying disease, bone marrow suppression, and therapy-related bleeding. There are few studies that specifically address transfusion in the pediatric oncology patient population. Recently, some recommendation papers or guidelines have been adopted in the literature.

In children with oncologic diagnoses or in patients undergoing hematopoietic stem cell transplantation who are critically ill or at risk of critical illness and who are hemodynamically stable, an Hb concentration of 7 to 8 g/dL is suggested as a threshold for red blood cell transfusion. For platelet transfusions, both the ICTMG and ASCO advocate a threshold of 10×109/L for prophylactic platelet transfusion, and children undergoing hematopoietic stem cell transplantation for sickle cell disease are at high risk for intracranial hemorrhage, so the platelet count should be at least 50×109/L in the period immediately after transplantation. There are no specific data for plasma transfusions in oncologic patients, and standard indications established for critically ill children are used in clinical practice. More limited to children with hematologic and oncologic disease, granulocyte transfusions may be considered in children with an absolute neutrophil count less than 500/mL or known neutrophil dysfunction and invasive clinical infection with demonstrated inadequate response to antimicrobial therapy.

In addition to selecting the type, timing, and dosage of blood product, the decision for leukoreduction, irradiation and washing is critical in pediatric oncology patients.

Further research surrounding indications, risk, benefits, and alternatives to RBC transfusion in critically ill children with oncologic diagnoses or undergoing hematopoietic stem cell transplant is sorely lacking. Although strong evidence-based guidelines for this patient population do not exist, given the morbidities associated with the receipt of blood products, practitioners should attempt to use restrictive transfusion strategies.

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Sp07

APPROACH TO PAIN MANAGEMENT

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International Association for the Study of Pain describes pain as 'An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (1). The phenomenon of pain is a common and underdiagnosed distressing symptom, resulting from the interaction between neural pathways and neurochemical mediators. An important group that suffers from acute and chronic pain -both at the beginning of the disease and in the later stages- are pediatric cancer patients. It is known that more than half of all children with cancer experience moderate to severe pain. Management of pain in childhood cancer plays an important role in patients' life quality and compliance with their treatment. Moreover, it is thought that uncontrolled pain may have negative effects on immune system functions, wound healing, tumor growth, and gastrointestinal functions through cortisole and neurochemokines that occur as a result of pain (2).

Pain can be categorized into three types for determining the etiology which may guide treatment choices:

Nociceptive pain: Tissue injury and inflammation cause activation of nociceptors by inflammatory mediators and activate neurons that transmit the pain. Bone metastasis and mucositis are examples of this group. 'Somatic Nociceptive pain' is typically well localized and described as sharp, aching, squeezing, stabbing, or throbbing. Visceral Nociceptive pain' is often described as dull or crampy.

Neuropathic pain is caused by nerve injury (resulting from compression, transection, infiltration, ischemia, or metabolic injury to the nerves) and can be described as burning, scratching, tingling or with numbness.

Nociplastic pain occurs without evidence of tissue or nerve damage. The mechanisms are not well understood. It is thought that dysfunction of the pain signals of central nervous system plays a role (1).

Assessment of the severity of pain in children is more difficult than adults and it is related to the child's age, cognitive ability and clinical condition. Observational– behavioral scales consider child's reaction to pain for younger children or cognitively impaired patients. The most common scales are FLACC (used for children < 3 years), facial expressions in the Wong-Baker pain scale for 3-8 ages, and numericale valuations in the Wong-Baker pain scale for children older than 8 years (3).

Multidisciplinary and individualized pain management incorporating pharmacological and non-pharmacological

(cognitive-behavioral and supportive therapies) can be more effective for pain. Pharmacological therapy varies depending on the child's age, pain intensity, drug's pharmacokinetics and response to previously administered agents. The World Health Organization analgesic ladder algorithm facilitates the choice of the appropriate drug. Acetaminophen and nonsteroidal anti-inflammatory drugs are the first choice for mild pain. Opioid agents (morphine, hydromorphone, oxycodone, hydrocodone, fentanyl, methadone) should be used for moderate to severe pain. Analgesics should be used orally whenever possible and adverse effects of opioids (eg, pruritus, constipation) should be carefully monitored.

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