HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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PEDIATRIC PRESENTATIONS

Sp01

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH CENTRAL NERVOUS SYSTEM TUMORS

Nurşah Eker

Marmara University Pediatric Hematology Oncology

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

Başak Adaklı Aksoy

Altinbas University

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

Deniz Tuğcu

Istanbul University, Istanbul Faculty of Medicine
Pediatric Hematology-Oncology

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)