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