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DERLEME MAKALESİ	REVIEW ARTICLE

Çocukluk Çağı Lenfoması ve Tedavisi

Childhood Lymphoma and Treatment

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ÖZET

Lenfoma, lenfoid dokulardan veya organlardan kaynaklanan üçüncü en yaygın çocukluk çağı malignitesidir. Vakaların çoğunda lenfomalar lenf düğümlerinden kaynaklanır. Lenf düğümü dışındaki lenf düğümlerinde kaynaklanan lenfomalar ekstranodal lenfomalar olarak sınıflandırılır. Çocukluk çağı lenfomaları iki ana kategoriye ayrılır: Hodgkin hastalığı ve Hodgkin dışı lenfoma. Hodgkin hastalığı vakalarının büyük çoğunluğu lenf düğümlerinden kaynaklanırken, Hodgkin dışı lenfoma bu yapıların içinden veya dışından da gelişebilir. Hızla büyüyen bu kanser için lenfomanın erken tedavisi son derece önemlidir. Cerrahın, hastalığın klinik semptomlarını tanıyabilmesi ve tanıya hemen dâhil olması zorunludur.

Anahtar Kelimeler: Çocuk, lenfoma, tedavi

ABSTRACT

Lymphoma ranks as the third most prevalent childhood cancer, emerging from lymphoid tissues and organs. Most commonly, lymphomas start in the lymph nodes. When lymphomas begin outside the lymph nodes, they're known as extranodal lymphomas. Childhood lymphomas fall into two main groups: Hodgkin's disease and non-Hodgkin's lymphoma. While Hodgkin's disease typically starts in lymph nodes, non-Hodgkin's lymphoma can begin either inside or outside these structures. Quick intervention is essential for this fast-growing cancer. Medical professionals, must recognize the signs quickly and play an active role in diagnosis.

Keywords: Child, lymphoma, treatment

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INTRODUCTION

Lymphoma represents the primary malignancy of lymphoid tissues. Two major groups of lymphomas, Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) differ in terms of their clinical manifestations, microscopic morphology, treatment and prognosis (1). NHLs represent a heterogeneous group of neoplasms with distinct pathologic and clinical characteristics (2). Nevertheless, NHL represents a relatively common malignancy in pediatric patients, ranking as the third leading cause of cancer-related mortality in this age group (3). Pediatric NHL is often diffuse, extranodal, high-grade, unique and confusing. Furthermore, the various childhood classifications used to classify it bear little relationship to our understanding of the cell's origin or behavior (4). To reduce the confusion caused by the multiplicity of classification systems for NHL, the National Cancer Institute has developed a histologic system known as the National Cancer Institute Staging (NCIWF), which defines three major subtypes of childhood NHL. Hodgkin's disease with Reed-Sternberg cells has been determined to be a predominantly malignant type of lymphoma in which various types of reactive inflammatory cells with varying degrees of fibrosis are present in the background (5). The initial report of HD in children was published by Thomas Hodgkin in 1832 and four additional cases were documented by Dorothy Reed in 1902. Subsequently, numerous studies have been conducted to examine the histology, incidence, epidemiology and prognosis of HD in children. It has been documented that HD is more prevalent in children residing in South America, the Middle East and Africa than in children in North America and Europe (1).

Classification of Treatments

The randomized Children's Cancer Group trial, designated CCG-551. The third comparison, which examined the biological subgroups of the LSA2-L2 protocol (vincristine, cyclophosphamide, prednisone, thioguanine, asparaginase, cytarabine, carmustine, methotrexate, daunorubicin, hydroxyurea) with treatment (drug-sharing method), yielded three primary findings:

- Differences in treatment efficacy are observed mainly in advanced disease
- Different chemotherapy regimens affect different NHL subtypes
- In advanced disease, differences in treatment efficacy were more pronounced with LBL (i.e., patients The frequency of relapses and event-free survival rates in patients with large-cell lymphoma did not differ significantly between regimens when treated with LSA2-L2) (6).

Previously, two distinct methodologies were employed for the categorization of childhood NHL treatment. The first method involved the classification of treatments according to histologic subgroups, while the second entailed the adjustment of treatment intensity in accordance with stage and supplementary criteria. An alternative model employed primary stratification for localized and advanced disease, with uniform treatment for localized disease of any histology. In contrast, subgroup-specific treatment was utilized for patients with advanced disease. Study conducted by the Pediatric Oncology Group demonstrated that even in patients with localized disease, different treatment strategies yielded disparate outcomes in histologic subgroups. The combination of 24 weeks of maintenance and nine weeks of induction yielded a positive outcome. For patients with LBL, this was not the case (7). Three principal subgroups of childhood NHL can be distinguished on the basis of treatment strategy. These are precursor B-cell (pB-LBL) and T-cell type LBL (T-LBL), Anaplastic large cell lymphoma (ALCL) and B-cell non-hodgkin lymphoma (B-NHL). The treatment protocols utilized in the management of ALL, based on the principle of prolonged continuous exposure to cytostatics, have demonstrated efficacy in the treatment of children with LBL. Chemotherapy regimens have been demonstrated to be more efficacious in the treatment of B-ALL/BL patients and also highly effective in the treatment of DLBCL patients (8).

Despite ALCL have comparable outcomes with both treatment strategies, the ALCL subtype has emerged as a distinct treatment group (9,10). This is mainly due to the fact that different prognostic parameters are important for treatment intensity stratification and that there is a higher probability of survival after treatment. The optimal therapy for a small but heterogeneous group of rare and currently less well-defined pediatric NHL subtypes, including relapsed peripheral T-cell/natural killer lymphoma (PTCL/NK), has yet to be determined (11). These and other rare subtypes of NHL, such as primary mediastinal (thymic) large B-cell lymphoma (PMLBL) and (juvenile) follicular lymphoma, are potential candidates for new subtype-specific therapies (11).

Diagnosis and Staging of Lymphoma

Getting the right diagnosis and understanding how far the cancer has spread are vital steps in choosing the best treatment plan. These steps also help identify different types of lymphoma that may need specific approaches. The step-by-step process for diagnosing lymphoma in children. It's important to note that any invasive tests can be risky, particularly for patients showing signs of superior vena cava syndrome or breathing problems due to chest tumors. In these urgent cases, doctors typically start with emergency steroid treatment, sometimes

combined with cyclophosphamide. This approach helps stabilize the patient while still allowing for an accurate diagnosis later. When dangerous fluid buildup occurs around the lungs or heart, drainage becomes necessary for completing the diagnosis.

The main tools for diagnosis are looking at cell structure, tissue patterns and cell surface markers. These methods usually provide enough information to properly classify patients and guide treatment decisions. Some cases, like unusual Burkitt lymphoma variants (as defined by WHO), require additional genetic testing for a definitive diagnosis (12).

Many children already have advanced disease when first diagnosed, often with cancer cells in their bone marrow or fluid collections. In these situations, doctors can often make an accurate diagnosis by examining cells under a microscope, using flow cytometry to identify cell types, and studying genetic patterns. When these methods aren't possible, a tissue biopsy becomes necessary. Most cases can be properly classified by examining cells directly from the tumor, studying tissue structure, and using special staining techniques on preserved tissue samples.

For proper treatment planning, it's crucial to distinguish between similar-looking types of lymphoma. Key distinctions include separating B-cell lymphoblastic lymphoma from Burkitt lymphoma or diffuse large B-cell lymphoma; telling apart T-cell-rich diffuse large B-cell lymphoma from nodular lymphocyte-predominant Hodgkin lymphoma; distinguishing primary mediastinal B-cell lymphoma from nodular sclerosing Hodgkin lymphoma and differentiating anaplastic large cell lymphoma from other T-cell/NK-cell lymphomas or Hodgkin lymphoma variants. Special tissue staining helps identify specific proteins like terminal deoxynucleotidyl transferase (found only in early B- and T-cell tumors) and bcl-6 (associated with germinal center cells) (13). Identifying specific chromosome changes can also be crucial. When traditional genetic testing isn't possible, fluorescence in situ hybridization (FISH) offers a reliable alternative for detecting chromosome changes in tumor samples or tissue sections (14). In most cases, specialized DNA testing can find specific genetic changes or unusual gene combinations (15). Recent research has shown that Burkitt lymphoma has a unique genetic signature that helps distinguish it from other types (16,17).

New diagnostic approaches, including detecting genetic changes in cancer cells and studying patterns of gene activity across the entire genome, are becoming increasingly valuable for identifying distinct subtypes and potential treatment targets. For this reason, when possible, it's

recommended to preserve additional tumor material(such as isolated cancer cells or frozen tissue samples) for future research.

Subgroup-spesific Treatment Protocols and Successes in Lymphoma

Lymphoblastic Lymphoma

Major clinical trials have shown survival rates of 60% to over 80%, even in children with advanced T-cell lymphoblastic lymphoma (18,19). Current treatment typically follows either the LSA2-L2 protocol or the Berlin-Frankfurt-Münster (BFM) approach, which was originally developed for acute lymphoblastic leukemia. Both methods involve four main phases: induction, consolidation, intensification and maintenance. The treatment combines several medications: steroids, vincristine, L-asparaginase, cyclophosphamide, methotrexate, anthracyclines, 6-mercaptopurine, cytarabine and 6-thioguanine. The main differences between these approaches are that the BFM method includes L-asparaginase and high-dose methotrexate (5 g/m² given intravenously over twenty four hours). Both treatments last 18 to 24 months. LSA2-L2 includes repeated courses with cyclophosphamide and anthracycline until treatment ends, while BFM uses simpler maintenance with oral 6-mercaptopurine and methotrexate. Relapses occur early or late in treatment, with few happening in between. Since most T-cell lymphoblastic lymphoma relapses happen within the first year after diagnosis, shorter maintenance therapy might be possible (20). The role of specific drugs in patient recovery remains unclear due to limited comparative studies. The POG-8704 trial showed L-asparaginase helped patients with T-cell lymphoblastic lymphoma when given at 20 mg/kg weekly after initial treatment (18). In major BFM studies, high-dose cytarabine didn't improve outcomes. Current BFM-based trials are testing whether dexamethasone works better than prednisone for lymphoblastic lymphoma, similar to improvements seen in leukemia patients (21,22).

Treatment intensity mainly depends on whether patients have early or advanced disease. Early-stage disease is rare. Most patients with B-cell lymphoblastic lymphoma achieve over 90% survival with less intensive treatment (modified BFM protocol) plus maintenance therapy. Whether treatment can be reduced further remains uncertain. POG trial patients with lymphoblastic lymphoma showed 63% survival with 24 weeks of maintenance after nine weeks of initial treatment, suggesting these cancers behave similarly to leukemia and benefit from maintenance therapy despite small tumor size.

For patients with clear brain involvement, radiation therapy (18-24 Gy) combined with LSA2-L2 or BFM chemotherapy effectively prevents brain relapse (23,24). For patients without brain involvement, treatment with spinal injections, methotrexate and high-dose methotrexate(0.5-5 g/m²) in early-stage disease without radiation isn't enough to protect the brain (20,23). The NHL-BFM 95 trial used four rounds of high-dose methotrexate and 11 spinal methotrexate doses without brain radiation. Patient survival and brain relapse rates were similar to previous trials, suggesting high-dose methotrexate might prevent testicular relapse as effectively as preventive radiation (19).

B-cell non-Hodgkin lymphoma

Chemotherapy options are adapted to the clinical and biological characteristics of BL and are also effective in other B-NHLs, particularly in patients with DLBCL. The most commonly utilized treatment regimens are based on the St. Jude Total B program, the French LMB in NHL trials, and the German-Swiss-Austrian BFM. The fundamental tenet of this approach is to sustain cytotoxic drug concentrations for an adequate duration to impact a substantial number of lymphoma cells during their vulnerable active cell cycle. This can be achieved through fractionated administration or continuous infusion (25). Other key principles include combining drugs with disparate mechanisms of action and minimal overlapping toxicity, administering high doses over time to maintain short treatment intervals and employing effective causes central nervous system (CNS) targeted therapy to address the pronounced invasive tendency of the CNS, particularly in the context of BL. Treatment strategies based on this principle include a triple-agent regimen comprising methotrexate, cytarabine and corticosteroids, with rapidly repeated 4-7 days of steroids, CP, VCR or HD-MTX, ifosfamide, etoposide, cytarabine and doxorubicin in addition to intrathecal therapy. In large multicenter trials, the event-free survival (EFS) rate has been as high as 90% (26,27,28). The importance of CP, VCR, and MTX was first demonstrated in the context of BL trials conducted in Africa. Although randomized comparisons are lacking, there is evidence of a dose-response effect, with MTX significantly reducing disease recurrence in patients with advanced disease and a large tumor mass after multiple MTX dose increases from 0.5 g/m² to 3.0, 5.0, and 8 to 0. g/m². The efficacy of the combination of high-dose cytarabine with etoposide has been demonstrated in patients who had failed conventional therapy (29).

The current highly effective regimen is associated with significant acute toxicity that cannot be reduced by post-chemotherapy Granulocyte colony stimulating factor (30). Advanced disease have an estimated risk of death from treatment-related complications of approximately 3%,

particularly during the initial phase of treatment (8,28). Severe gastrointestinal mucositis and severe neutropenia, primarily but not exclusively caused by HD MTX, are significant acute toxicities that contribute to serious infections in a synergistic manner. Another significant risk in the early stages of treatment is the occurrence of metabolic disorders associated with Acute tumor cell lysis syndrome (31).

Chemotherapy alone, including systemic methotrexate at a risk-adjusted dose of 0.5-8 g/m² and triple intrathecal therapy, rarely CNS relapse in patients without overt CNS disease at diagnosis (23,26,32). In patients with resected local tumors other than head and neck tumors, intrathecal therapy may be unnecessary. Patients with overt CNS involvement have worse outcomes than patients with CNS-negative and advanced disease, including bone involvement. To date, no randomized trials have been conducted to evaluate the efficacy of cranial irradiation in patients with CNS-positive (B-NHL). In recent studies of patients with CNS-positive B-NHL, the EFS rate was 70% with LMB and BFM protocols that included 3 g/m² HD cytarabine and 24 hours of intravenous 8 g/m² and 5 g/m² HD MTX, as well as intensive intrathecal triplet therapy with lumbar puncture (LMB) or fractionated intravenous (28,33). These results are comparable to those of a previous LMB study in CNS-positive patients receiving adjuvant cranial irradiation. The occurrence of testicular recurrence is infrequent when HD MTX treatment strategies are employed (20,26).

Lymphoma Treatment

In contrast to classical HL, there are no large-scale randomized controlled trials that have been conducted in the treatment of NLPHL. Treatment recommendations are based on case series (34). Although radiotherapy is a common treatment in early adulthood, it is generally avoided in childhood due to its long-term side effects (35,36). Complete surgical resection without adjuvant chemotherapy has been demonstrated to result in long-term remission in patients with early-stage localized NLPHL. The administration of combination chemotherapy without RT has been associated with favourable outcomes in terms of disease progression and side effects (36,37). In cases of advanced disease, combination treatment programs similar to those used for classical HL are recommended, with planning based on response (38,39). Given the expectation that patients will progress to non-Hodgkin lymphoma (NHL) in the subsequent cycle, treatments for NHL are initiated. In adults, rituximab, which is effective against CD20, is used in combination with chemotherapy (40). A case of remission with rituximab in a child who failed to achieve remission with CT and RT has been reported (41).

The monitoring of adverse events is of significant importance in the context of patients who have undergone treatment for Hodgkin's lymphoma, given the extended life expectancy that these patients typically enjoy. It is of particular importance to monitor cardiovascular adverse events, as they represent the common cause of non-cancer related mortality in this patient group. It is recommended that these patients undergo routine follow-up and screening, given the observed increase in treatment-related cardiovascular adverse events in later years (42). The use of 3DE evaluation is advised in cancer survivors, as it provides superior insight into systolic function compared to conventional echocardiograp hy (43). In the 1950s, it became evident that Hodgkin's disease could be successfully treated with radiation therapy to the affected regions. Until the 1970s, children and adults were treated similarly. However, the MOPP (mechlorethamine/nitrogen mustard, vincristine/oncovin, procarbazine, prednisolone) chemotherapy regimen, developed in the late 1960s, was based on the principle that certain drugs are effective against the tumor. This approach involved the use of antitumor drugs with different mechanisms of action and non-overlapping toxicities. The regimen is widely used due to its convenient suitability (44). Notwithstanding the favorable outcomes associated with the MOPP protocol, novel therapeutic avenues are being pursued due to the potential for late effects, including acute myeloid leukemia in pediatric patients and infertility. In the 1970s, an ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) protocol was developed that did not entail a significant risk of secondary leukemia or infertility (45). The ABVD protocol has been employed with greater frequency in pediatric patients, given that the treatment is more efficacious in adults than the MOPP regimen. Furthermore, the ABVD protocol possesses notable characteristics pertaining to cardiac and pulmonary damage, which must be taken into account when administering this treatment to pediatric patients.

Author's contribution to the work:

Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing: Altay Babacan; Conceptualization, Project administration, Writing – original draft, Writing – review & editing: Feray Ferda Şenol; Conceptualization, Data curation, Resources: Serdar Ümit Sarıcı; Investigation, Methodology, Supervision: Özlem Aytaç

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Conflict of interest

Regarding this study, the authors and/or their family members have no relationships or potential conflicts of interest, such as membership or association with scientific and medical committees, consultancy, expert witness roles, employment in any company, shareholding, or similar situations.

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Ethics Statement

This article does not contain any research involving humans or animals requiring ethical approval.

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