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THE HIGH RATE OF SUCCESSFUL TREATMENT FOR MALIGNANT LYMPHOMA IN CHILDREN

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Summary

Malignant diseases are one of the most common causes of mortality in children in Europe and America. In the past ten years, considerable advancement has been achieved in both the diagnosis and treatment of these diseases, malignant lymphoma in particular. With the introduction of new therapeutic modalities (new combinations of cytostatics, radiotherapy, surgery, monoclonal antibodies, and bone marrow transplantation), a high rate of long-term remission and recovery is now possible to achieve.

KEY WORDS: *malignant lymphoma, children, treatment*

VISOKA STOPA USPJEŠNOG LIJEČENJA ZLOĆUDNIH LIMFOMA U DJECE

Sažetak

Maligne bolesti su jedan od vodećih uzroka smrtnosti djece u Europi i Americi. Posljednjih desetak godina učinjen je bitan napredak kako u dijagnostici tako i u njihovom liječenju, naročito u liječenju malignih limfoma. Uvođenjem novih metoda liječenja (nove kombinacije citostatika, zračenja, kirurškog zahvata, monoklonskih antitijela te transplantacije koštane srži) i u ovih bolesnika danas je moguće postići visok postotak dugotrajnih remisija i izlječenja.

KLJUČNE RIJEČI: *maligni limfomi, djeca, liječenje*

Malignant lymphomas are the third leading malignancy in children, immediately following leukemias and brain tumors, accounting for 13% of tumor diseases in children. Malignant lymphomas are characterized by neoplastic proliferation of cells that are histogenetically related to those normally found in lymph nodes. Malignant lymphomas are classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphomas (NHL), the former showing a slightly higher prevalence (7%) than the latter ones (6%) (1).

HODGKIN'S LYMPHOMA

Hodgkin's lymphoma is a neoplastic disorder originating from lymphatic tissue. It is characterized by the presence of pathognomonic malignant Reed-Sternberg and Hodgkin cells in a lymph node or lymphatic tissue. It is a relatively rare disease with an incidence of 2.6-5.7 *per* million children *per* year. Hodgkin's lymphoma rarely occurs before age 5, while the age adjusted prevalence curve shows a bimodal pattern with two peaks: first between age 15 and 30, and sec-

ond between age 45 and 55. Until age 7, the disease shows a high male predominance (M:F ratio 10:1), to equalize in male and female children after age 12 (2).

The etiopathogenesis of the disease remains unknown. The implication of Epstein-Barr virus (EBV) in its development has been postulated. EBV fragments are found in Reed-Sternberg cells and Hodgkin cells (a mononuclear variant of Reed-Sternberg cells), mostly in the histological subtype of mixed cellularity and extremely rarely in the histological subtype of lymphocytic predominance. The disease develops more frequently in individuals with congenital or acquired immunodeficiencies, autoimmune diseases, and hypogammaglobulinemias. It could be postulated that Hodgkin's lymphoma is caused by some as yet unknown agent(s) and develops only in "susceptible" individuals. The course of the disease depends on the Reed-Sternberg cell and Hodgkin cell count. More "reactive" cells and less Reed-Sternberg and Hodgkin cells are detected in prognostically more favorable histological types of the disease, and *vice versa* in the histological type of higher malignancy. Chromosomal analysis of the tissue involved reveals two cell populations: one with normal karyotype, and the other frequently displaying hypotetraploidy, belonging to malignant cells. Molecular biology failed to clarify the origin of the malignant cell on cell line analysis in Hodgkin lymphoma. Cellular immunity is diminished; T lymphocyte count is normal but their function is impaired (skin reaction to tuberculin and graft *versus* host (GVH) reaction fail), making these patients more prone to the development of infections such as tuberculosis, fungal infections, and viruses (especially herpes zoster and varicella); humoral immunity is not impaired, however, the production of antibodies may be diminished in advanced stages, after chemotherapy and radiotherapy in particular.

Hodgkin and Reed-Sternberg cells produce cytokines that may be responsible for the signs and symptoms of the disease, i.e. interleukin 1 (IL-1) for lymphoproliferation, temperature elevation, and night sweat; IL-2 for cellular immunodeficiency; IL-5 for eosinophilic infiltration; IL-6 for thrombocytosis; IL-9 for lymphoproliferation; tumor necrosis factor (α and β) for weight loss; and GCSF for myeloproliferation.

Hodgkin's disease generally first involves a single lymph node to disseminate *via* lymphatics to adjacent lymph nodes and organs; hematogenous dissemination may also occur, when the spleen is infiltrated first upon the disease crossing the diaphragm line (typical for histological types of mixed cellularity and lymphocytic depletion), determining the clinical picture (the neck, mediastinum, and abdomen). The disease mostly manifests as enlargement of one or more lymph nodes (hard and painless) on the neck (70%), axillae (20%) and inguinal region (10%). Mediastinal lymph nodes are involved in some 60% (the leading symptom is persistent, dry, unproductive, gradually worsening coughing), and retroperitoneal lymph nodes in 25% of patients. In abdominal localization, the main symptoms are undefined pain in the abdomen, occasional constipation and diarrhea, along with general symptoms of weight loss, night sweat, elevated body temperature, and pruritus. In this localization, the disease is generally detected on operative procedure for suspected acute abdomen. Some patients (40%) have general symptoms, i.e. elevated temperature, night sweat, pruritus and weight loss, which imply a poorer prognosis.

When Hodgkin's lymphoma is suspected, lymph node biopsy for cytomorphological analysis is done first, followed by lymph node biopsy for histopathology to make definitive diagnosis. Two classifications are currently in use: RYE classification distinguishing four disease subtypes: lymphocyte predominance, nodular sclerosis, mixed cellularity, and lymphocyte depletion; and REAL (revised European American) classification distinguishing nodular form of lymphocyte predominance and classic Hodgkin's lymphoma (nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich classic Hodgkin's lymphoma). According to some authors, nodular sclerosis type II has a significantly poorer prognosis than nodular sclerosis type I. The disease activity is indicated by erythrocyte sedimentation rate (ESR), copper, and lactate dehydrogenase. Diagnostic work-up should include EBV serology, chest x-ray, computed tomography of the neck, chest, abdomen and pelvis, positron emission tomography (PET), skele-

ton scintigraphy, bone marrow puncture and biopsy, gallium scintigraphy, and technetium scintigraphy of the skeleton. ECG, ECHO, pulmonary function tests, thyroid hormones, LH and FSH should also be done.

Upon making the diagnosis, the stage and extent of the disease should be assessed according to Ann Arbor classification: stage I – one lymph node region (I) or one extralymphatic organ or site (IE) involved; stage II – two or more lymph node regions on ipsilateral side of diaphragm involved (II) or localized involvement of one extralymphatic organ or site and one or more lymph node regions on ipsilateral side of the diaphragm (IIE); stage III – lymph node regions on both sides of diaphragm involved, which may be accompanied by involvement of the spleen (IIIS) or localized involvement of one extralymphatic organ or site (IIIE) or both (IIISE); and stage IV – diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without lymph node involvement. When the patient is free from the symptoms of 1) elevated temperature, 2) night sweat, 3) pruritus, and 4) unexplainable weight loss >10% in the last 6 months, the stage of the disease is designated with A; when one or more of these symptoms are present, it is designated with B.

The stage of the disease is the most important prognostic factor. Other unfavorable prognostic factors include extranodal disease, spleen infiltration, precipitated ESR, and histological picture of mixed cellularity, lymphocyte depletion and nodular sclerosis type II (3).

The treatment of Hodgkin's disease includes chemotherapy with low dose/small field radiotherapy (not administered in early stages). Polychemotherapy is exclusively used to reduce cumulative toxicity of particular cytostatics and to prevent the development of tumor resistance; patients receive 2, 4, 6, or occasionally even 8 courses. The following protocols are most frequently applied: OPPA (Adriamycin, vincristine, procarbazine, prednisone); OEPA (Adriamycin, vincristine, etoposide, prednisone); COPP (cyclophosphamide, vincristine, procarbazine, prednisone); COPDIC (cyclophosphamide, vincristine, dacarbazine, prednisone); IEP (ifosfamide, etoposide, prednisone); ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine); CEP (CCNU, etoposide, prednimustine); Dexa-BEAM (dexamethasone, BCNU, melphalan, etoposide, cytosine arabinoside); and radiotherapy (20 Gy upon residual tumor area after chemotherapy) (4-6).

Good therapeutic outcome is achieved in 95%-100% in stage I and IIA, 90%-95% in stage IIB and IIIA, and 80%-90% in stage IIIB, IVA and IVB. In case of disease relapse, more aggressive and toxic polychemotherapy with radiotherapy is administered: 1) 6 courses MOPP (chlorometine, vincristine, procarbazine, prednisone)/ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) + radiotherapy; 2) 2 courses IEP/ABVD + radiotherapy; 3) 2 courses IEP/ABVD + 2 courses Dexa-BEAM + radiotherapy; 4) IEP + ABVD + COPP + IEP + radiotherapy; 5) 2 courses IEP/ABVD/COPP + radiotherapy, possibly + 2 CEP courses; 6) 2 courses IF + VRB (ifosfamide + vinorelbine + G-CSF); and 7) 2 courses VRB + GEM (vinorelbine + gemcitabine + G-CSF). In case of resistant disease, megatherapy (myeloablative therapy) + autologous bone marrow or peripheral stem cell transplantation) is used. The efficacy of experimental therapy, i.e. immunotherapy with the use of anti CD20 monoclonal antibodies, rituximab (Mabthera), is being investigated, with promising results reported in the histological type of lymphocytic predominance (7).

Successful management of Hodgkin's lymphoma is accompanied by complications that may be early and late. The most common early complications include: (a) acute radiotherapy effects that are reversible and harmless (erythema, hyperpigmentation of irradiated skin, possible mild gastrointestinal discomforts, thrombocytopenia, granulocytopenia); and (b) direct chemotherapy side effects (nausea, vomiting, neurotoxicity (vincristine), cardiotoxicty (Adriamycin), pulmonary toxicity (bleomycin), and infections). Late complications include impaired growth of bones and soft tissues; sterility (procarbazine in male, and pelvis irradiation in female children); hypoparathyroidism (neck irradiation – thyroid adenoma, carcinoma); cardiopulmonary complications (pneumonitis and pulmonary fibrosis associated with chemotherapy and radiotherapy-irradiation and/or bleomycin, and pericarditis and pancarditis associated with irradiation); infections (herpes zoster, varicella,

fungal infections, *Pneumocystis carinii*); and secondary malignant diseases (leukemias associated with alkylating chemotherapeutics, and solid tumors associated with irradiation) (8).

Improvement of therapeutic results while reducing the level of therapeutic toxicity and rate of early and late complications remains the main goal of treatment. Future developments will focus on therapy individualization to increase the probability of cure with minimal long-term side effects (9).

NON-HODGKIN'S LYMPHOMAS

Non-Hodgkin's lymphomas (NHL) are clonal malignant diseases of lymphocytes, i.e. a heterogeneous group of malignant proliferations of lymphoid tissue. They are characterized by rapid growth, early dissemination, and high grade of malignancy. In NHL, malignantly altered lymphocytes occur in lymph nodes, and less frequently in other organs; proliferation of atypical histiocytes is found in a minor proportion of patients. The disease heterogeneity manifests by variable clinical picture, laboratory findings, histology findings, immune origin of malignant cells, therapeutic response, and disease prognosis. The main characteristics of NHL in children are: (a) diffuse histology; (b) undifferentiated cytology; (c) predominantly extranodal localization; and (d) extensive dissemination at the time of diagnosis in more than 75% of patients (10).

NHL account for 7% of all malignancies of childhood. Approximately 500 new pediatric cases are diagnosed in the USA *per* year. The disease is found all over the world; however, the highest prevalence has been recorded in equatorial Africa (50% of all tumor diseases of childhood) and an increased prevalence in the north-east of Brazil, while being relatively rare in Japan. NHL is extremely rare in children younger than 2 years, then its prevalence gradually increases during childhood to reach peak at age 7-10. In male children, the prevalence of NHL is 2- to 3-fold that in female children (11).

The etiopathogenesis of NHL has not yet been fully elucidated. A number of factors are involved, such as impaired regulation of the immune system, gene abnormalities, etc. In most cases, it occurs without previous overt impairment of the lymphocyte system. An increased risk of NHL has been observed in patients with congenital (severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome) and acquired (HIV/AIDS) immunodeficiencies, in patients with immunosuppression (following solid organ transplantation or allogeneic stem cell transplantation), autoimmune diseases, and individuals exposed to some chemical carcinogenic agents. EBV is considered to cause Burkitt's lymphoma, and may also be associated with the occurrence of other lymphatic system disorders and lymphomas in transplanted patients. The most common initial symptoms in children with NHL are listed in Table 1 (12-14).

Table 1.

MOST COMMON INITIAL SYMPTOMS IN CHILDREN WITH NON-HODGKIN'S LYMPHOMA (NHL)

- painless lymph node enlargement
- dyspnea, cyanosis, retrosternal pain (mediastinal NHL)
- constipation, abdominal pain, diarrhea, anorexia, melena, palpatory resistance (abdominal NHL)
- pain and pressure in bones (bone NHL)
- headache, seizures (central nervous system NHL)
- hepatosplenomegaly (leukemic transformation of NHL)

Cytological and especially histopathological analysis of tumor material are of high diagnostic relevance. According to the World Health Organization classification, NHL in children is categorized into four main types: (a) B-NHL (Burkitt's lymphoma), 40%; (b) DLBCL (diffuse large cell B lymphoma), 20%; (c) LL (lymphoblastic lymphoma), 30%; and (d) ALCL (anaplastic large cell lymphoma), 10% of cases.

There is a high correlation between karyotype abnormalities and biological features of NHL, including histological subtype, immunophenotype, histological progression, and clinical characteristics of the disease. Multi-center studies of the correlation between chromosomal abnormalities and therapeutic outcome have revealed the abnormalities of chromosome 17, trisomy 18, chromosome 5 abnormalities, trisomy 6 and trisomy 5 to be associated with a shorter mean survival. In addition, resistance to chemotherapy was more common in patients with monosomy 7 or 17 (15).

Upon making the diagnosis of NHL (with immunophenotyping and cytogenetic analysis),

Table 2.

CLINICAL CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS (NHL) IN CHILDREN

Stage I	single tumor (extranodal) or single anatomic region (nodal) excluding mediastinum or abdomen
Stage II	single tumor (extranodal) with regional lymph node involvement, two or more lymph node regions on the ipsilateral side of diaphragm, operable primary gastrointestinal tumor with or without mesenterial lymph node involvement
Stage III	two individual tumors on contralateral sides of diaphragm, two or more lymph node regions superior or inferior to diaphragm, all primary intrathoracic tumors, all extensive inoperable abdominal tumors
Stage IV	any of above stages with initial involvement of bone marrow and/or central nervous system

the following work-up should be done: ESR, complete blood count, liver tests, urea, creatinine, LDH, lung x-ray, CT/NMR of the head, neck, mediastinum, abdomen and pelvis, PET, gallium scintigraphy, skeleton scintigraphy (suspected bone lesions), multiple bone biopsies, and cerebrospinal fluid (CSF) testing to assess the extent (stage) of the disease (Murphy classification) (Table 2).

The treatment of NHL includes operative procedure, radiotherapy, chemotherapy, and immunotherapy (monoclonal antibodies). Operative procedure is mostly used to obtain tumor tissue for histopathology, as radical surgery is rarely possible to perform. Radiotherapy is infrequently employed because of its local effect against mostly generalized disease. Thus, chemotherapy is the treatment of choice, the intensity and length of treatment depending on the type and stage of NHL (16).

In T-NHL, therapeutic protocols for the treatment of acute lymphatic leukemia are used: intensive therapy with 10-15 different cytostatics with central nervous system (CNS) radiotherapy (as a prophylaxis for CNS disease) for 8-12 months, followed by therapy to maintain the achieved remission for another 12-16 months. The first complete remission is achieved in 95%, and cure in 80%-85% of patients (17).

In B-NHL, short-term chemotherapeutic courses for 5-7 days are used; the patient receives 7-8 different cytostatics, some of them at high doses, which results in profound myelosuppression accompanied by severe, frequently life-threatening crises. Depending on the stage of disease, 2, 4 or 6 courses are administered over 2, 4 or 6 months, thus completing the treatment. The first complete remission is achieved in 90%-95% and cure in 85%-90% of patients (18,19).

In case of Ki-1 anaplastic large cell lymphoma, patients receive 3 or 6 courses of chemotherapy (similar to therapy for B-NHL), depending on the stage of disease. The first complete remission is achieved in 90%-95% and cure in 75%-80% of patients (60%-100%, depending on the stage of disease).

In case of the disease relapse, the protocols for NHL relapse are used, including administration of high doses of cytostatics, followed by bone marrow or peripheral stem cell transplantation if second remission has been achieved.

Patients with NHL refractory to standard chemotherapy are administered target therapy with monoclonal antibodies: anti CD20 – rituximab (Mabthera); anti CD22 – epratuzumab in BL and DLBCL; anti HLA-DR – apolizumab; anti CD52 – ampath 1 – alemtuzumab in ALCL. The best response was recorded with the use of anti CD20 antibodies in B-NHL; therefore trials with its use in the induction stage of B-HNL to reduce the toxicity of standard chemotherapy have been under way. It has also been investigated whether target therapy with antibodies along with standard chemotherapy could improve the outcome in B-NHL associated with poor prognosis; preliminary results appear to be quite encouraging. Accordingly, the main therapeutic modalities for NHL may in the near future include a combination of target therapy with monoclonal antibodies and chemotherapy (20,21).

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