Pediatric Non Hodgkin's Lymphomas

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Abstract

Pediatric non-Hodgkin lymphoma (NHL) is a diverse collection of diseases, and results from malignant proliferation of lymphoid cells and immune system. NHL involves throughout the body, but bone and primary central nervous system (CNS) lymphomas are its rare presentations. The incidence of NHL in childhood differs according to age and geographic area, but overall constitutes 8–10% of all malignancies in children between 5–19 years of age. The preferred pathologic and molecular biology classification for NHL is based on currently recognized histologic (morphologic), immunophenotypic, and genetic features, and their clinical presentation and course. The clinical manifestations of NHL in children depend on pathological subtype and primary sites of disease. Abdomen and mediastinum are the most frequent primary sites of involvement. Most centers use st. Jude staging system and diagnostic workup. Most patients present with advanced stage and systemic disease. According to pathophysiology of childhood NHL, treatment strategy is based on extent of dissemination and requires attention to emergent complications. Modern treatments have caused dramatic improvement in childhood NHL. We need well conducted international studies in all parts of the world to increase our knowledge to acieve better outcome and prevent late effects in children.

Keywords: Non-Hodgkin Lymphoma, Survival, Chemotherapy.

Non-Hodgkin's lymphomas (NHL) in childhood are characterised by predominant extranodal disease and a rapid tumoral growth and dissemination, especially into bone marrow and central nervous system (CNS).[1-3] Malignant lymphoma is the third most common malignancy in paediatrics, and accounts for about 15% of all malignancies in people younger than 20 years.[2-6] The etiology is unknown, but some studies have shown its relation with viral infection (EBV, HIV), inherited immune deficiency (ataxia-telangiectasia, XLP-agammaglobulinemia), some drugs (phenytoin) and exposure to radiation and environmental hazard (pesticide).[6-14] Abdomen and mediastinum are the most frequent sites of primary involvement, but many other sites can be involved. Diagnostic workup and staging system according to st.Jude research hospital should be used to estimate extent of disease, prognosis, and best treatment strategy.[15]. Rapidly growing or bulky tumors can cause severe metabolic complications, which may be life threatening such as tumor lysis syndrome.[16] Mediastinal tumors may cause compression of the great vessels in chest (superior vena cava syndrome), with plethora, swelling of the neck, face, and upper extremities. Esophageal compression may lead to dysphagia.[16-20] In affected individuals, thoracentesis may be both therapeutic and diagnostic, obviating need for biopsy. Initial laparotomy and thoracotomy should be avoided as diagnosis can be made by cytological examination of fluid effusion or tumor percutaneous needle biopsy. Three major histological types are encountered; frequency, predominant sites, immunological and cytological characteristics are described:

1) Burkitt (50-55%): abdomen, Waldeyer ring; B-cell CD20+, Sig+, t (8-14) or variant t (2-8) or t (8-22),

2) Lymphoblastic (25-30%): T-cell, mediastinum; rarely B-precursor, bone or (sub) cutaneous sites,

3) Large cell lymphomas with 2 major sub-type (~20%):

- Anaplastic large cell lymphoma: positivity of CD30 (Ki1); t (2-5); clinically: usual node involvement, often painful and inflammatory; frequency

of skin involvement and of general symptoms.

- Large B-cell lymphoma; abdomen, thorax, node, bone; B-cell CD 20+, Sig+. [17]

NHL is a very fast growing tumor and has to be considered as a therapeutic emergency.[1,18] Once the positive diagnosis has been made, a speedy assessment of staging and general evaluation, especially renal function, is needed to permit treatment to begin with as little delay as possible. Tumor lysis syndrome must be prevented by hyperhydration and uricolytics (allopurinol, urate-oxydase), + alkalinisation. Strict monitoring of water and electrolyte balance must be performed.[17-21]

Treatment

Except in very few specific situations, surgery and radiotherapy do not have any more place in the treatment of childhood NHL. The key word for treatment is *CHEMOTHERAPY*. Its modalities and intensity have to be adapted to the type of lymphoma and to its extent.[20-34]

1) B-cell lymphoma

Burkitt NHL is characterised by a short cell cycle, a high proliferation rate, large tumours, an early dissemination especially in CNS, and early relapses within one year after diagnosis. So, general principles of treatment are: combination of drugs delivered in fraction or in continuous infusion, intensive chemotherapy adapted to tumor burden, short intervals between courses, short duration and CNS prophylaxis. Serum LDH level, although non-specific, is a good marker of tumor burden and proliferation rate, and has a prognostic value in many studies.[21-29]

The main 3 drugs are: cyclophosphamide (CPM), high dose methotrexate (HD MTX), and Cytarabin (Ara-C). Other important drugs are: vincristine (VCR), prednisone, adriamycine, etoposide (VP16), and ifosfamide. They are delivered in various associations as short pulse courses. L3 ALL shares the same characteristics with Burkitt's NHL and is included in the same protocols. Large B-cell lymphomas seem to benefit from protocols identical to Burkitt, but they can relapse later than one year.[22-30]

In Europe, 2 national groups, French and German, had conducted multicenter studies since 1981 which resulted in considerable improvement of cure rates.[21-24]

a) French LMB studies.

Four consecutive studies (LMB 81, 84, 86, 89) were conducted by SFOP (French Pediatric Oncology Society). General scheme of the protocol is: prephase with low dose of VCR, CPM, and prednisone (COP course) which generally induces a good tumor reduction and allows to solve metabolic and general problems without aplasia, 2 induction courses based on fractionated HD CPM and HD MTX (COPAD M courses), 2 consolidation courses based on Ara-C in continuous infusion, maintenance whose duration was progressively reduced along the studies, CNS prophylaxis based on HDMTX (3g/m2 in 3h infusion) and intrathecal injections (IT) of MTX started early and continued during treatment, CNS treatment by higher dose of MTX (8g/m2 in 4 h), HD Ara-C (3g/m2 x 4), triple IT and cranial irradiation.[27,34]

Along with the studies; duration of treatment was reduced, toxic death rate decreased partly due to increased experience of the investigators, bad prognostic factors were identified and more intensive treatment was adapted to them: no tumor response after the 1st week of treatment, no CR with proven viable residual mass after the 3rd course of treatment, and CNS involvement.[27,34-37]

In the LMB 89 protocol which is just finished, Burkitt and large B-cell lymphomas were included and patients were classified in 3 risk groups which received treatment of increased intensity. The analysis of 566 patients included between July 1989 and June1996 showed a 3-year overall survival of 93% + 2 and event free survival (EFS) of 92% + 2. By stage, EFS was: 96% + 3 for 122 stage I+ II, 93% + 3 for 279 stage III, 88% + 2 for 165 stage IV+ L3-ALL patients, and 79% + 8 for 62 patients with initial CNS involvement.[27,34]

The new international study FAB LMB 96 (SFOP + UK CCSG + US CCG) is a randomised trial which will study the possibility of more reduction in treatment, especially CPM dosage (due to the problem of sterility in boys), and its duration.[28,33]

b) BFM protocols.

Along with 4 consecutive BFM studies (81, 83, 86, 90), treatment intensity was progressively increased, treatment duration reduced, and CNS irradiation withdrawn. In the last study (BFM 90), treatment was also stratified on 3 risk groups (a little different from those of the French study). Re-

sults presented in June 1996 (Lugano) on 329 patients included between 4/1990 and 9/1994 were as follows: the estimated EFS at 5 years was 91% ± 2 for all patients and according to risk groups: 100% for 56 patients with resected disease, 97% ± 2 for 130 patients with extra-abdominal non-resected disease or abdominal stage III with LDH<500, and 79% ± 3 for 140 patients with abdominal stage III and LDH > 500 or with bone marrow and/or CNS involvement.[21,32]

The most remarkable data is the increase of EFS from 50% to 80% for patients with stage IV and L3 ALL (study 86) and those with abdominal stage III and LDH > 500 (study 90) when MTX was increased from 0,5 to 5 g/m^2. In a study started recently, a randomised trial concerns modality of administration of HD MTX: 24 h versus 4 h.[32]

c) Other protocols.

The third largest series on Burkitt's is the POG'S series. Currently this group is testing the value of Ifo-VP16 in advanced stages. The other publications concern smaller number of patients generally from one institution (Boston, Schween, 1991, Milan, Gasparini, 1993; NCI, Magrath 1996).[31,35-39]

2) Non B-cell lymphomas

This concerns mainly T-cell lymphoblastic lymphomas. The most successful treatments are identical or similar to those of high risk lymphoblastic leukemia, such as the LSA2L2 protocol (and those derived from it) and the BFM protocol. Treatment has to be intensive, semi-continuous, lasting 1 to 2 years, including CNS prophylaxis and numerous drugs (corticosteroids, VCR, CPM, anthracyclins, MTX, VP16, Ara-C, asparaginase, 6-mercaptopurine or/and 6-thioguanine).[20,38-42]

Protocols are stratified according to the stage. Among the protocols, the BFM 90 protocol was using an 8-drug induction including prednisone over 9 weeks followed by an 8-week consolidation with Methotrexate 4x5 g/m^2. Patients with stage I and II disease received maintenance therapy (6-mercaptopurine daily/methotrexate weekly, both orally) for a total duration of 24 months. Patients with stage III or IV disease received, after consolidation, an additional 8-drug reinduction over 7 weeks and cranial radiotherapy (12 Gray (Gy)) for prophylaxis. Patients received intensified chemotherapy if tumour regression on day 33 of induction was <70% or when vital residual tumour was present after the induction, but no local radiotherapy. Treatment results show a 92 % EFS for stage I and II and an 82 % EFS for stage III or IV.[32]

The French LMB 96 protocol showed similar results with a 90% 5-year overall survival.

In the European LB 02 protocol it was agreed that the BFM 90 was the reference arm for treatment of non B-cell lymphomas with the exception that prophylactic cranial irradiation can be omitted in CNS-negative patients. In vitro and in vivo data demonstrated that compared to prednisone, dexamethasone is associated with increased antilymphoblastic activity and enhanced CNS penetration. In the LB02 trial, patients with T-LBL entered a randomised trial comparing the efficacy and the toxicity of dexamethasone and prednisone during remission induction.[34]

3) Large cell lymphomas

Depending on the countries, treatments are based either on an intensive and short chemotherapy regimen derived from Tt for B-NHL, or on a less intensive but more prolonged chemotherapy.[29,30]

The ALCL99 trial, a large international trial, based on the NHL-BFM90 aimed to compare the efficacy and safety of two doses and modes of administration of high dose methotrexate (HDMTX), and to study the impact of adding vinblastine in patients at high risk of failure. The POG9315 trial aimed to assess the effect of incorporating into APO (doxorubicin, prednisone, vincristine) 8 courses of HDMTX by HDAra-C. The CCG5941 was based on a 48-week intensive multiagent T-cell lineage CT.[29,36]

Overall survival ranged from 80% to 92%. Given the good results obtained in terms of EFS, the short duration of the treatment and the lower cumulative doses of drugs known to be associated with a risk of long-term toxicity, such as alkylating agents, etoposide and anthracyclines, compared to other pediatric and adult protocols, ALCL 99 protocol is one of the most attractive current treatment regimens.[29,36]

One of the major developments in recent years has been identification of the high risk of failure associated with the presence of circulating cells in blood and bone marrow harbouring the NPM-ALLK fusion gene detected by PCR at diagnosis. This technique allows the definition of a group of patients at high risk of failure that might benefit from an early

Tt intensification.[38]

Another important recent development is the description of both B and CTL immune response to ALK in ALK+ ALCL, as well as, showing the correlation of the presence of anti ALK antibody with the presence of circulating cells. This finding provides valuable information for developing future immunotherapeutic options for ALCL.[39-44]

4) Bone marrow transplantation

Because of high cure rate, there is no indication for patients in first complete remission. There is neither indication for patients with evolutive disease. But it must be considered for patients who achieved partial remission and for patients who relapsed and responded to the second line chemotherapy.[23,25,45]

Conclusion

Dramatic improvement has been obtained in the past ten years in cure rate of children with NHL, particularly B-cell lymphomas. This is due in great part to prospective well conducted national multicenter studies including a large number of patients which increase the knowledge of the diseases, identify new prognostic factors, and allow for a better use of chemotherapy.

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