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Paediatric Update

Non-Hodgkin's Lymphoma

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INTRODUCTION

ALTHOUGH THERE are still unanswered questions about the biology and therapy of Non-Hodgkin's Lymphoma (NHL), much progress has been made in understanding the different diseases grouped under the term 'Non-Hodgkin's Lymphoma' and in their treatments. Before 1970, the majority of children with NHL would die. Now, the majority are cured, with a cure rate above 75%.

EPIDEMIOLOGY-PATHOGENESIS

NHL are seen at any age but are uncommon before 2 years of age. There is a male predominance (2:1 to 3:1) which is more pronounced in Burkitt's lymphoma. The annual incidence is 7 cases per million children in the U.S. and in Europe, making NHL the third most common childhood malignancy in these countries. Incidence rates and distribution of histological subtypes are not constant throughout the world. This is evident for Burkitt's lymphoma. In equatorial Africa, Burkitt's lymphomas represent 50% of all childhood cancers and the estimated incidence is 5–10 cases per 100 000 children below the age of 16 years.

Individuals with congenital or acquired immunodeficiences are at increased risk of developing NHL (ataxia telangiectasia, Wiskott–Aldrich syndrome, X-linked lymphoproliferative disease, AIDS or patients receiving immunosuppressive therapy after organ transplant). However, the spectrum of lymphoproliferation, as well as the association with Epstein–Barr virus (EBV), depends on the nature and the severity of the underlying immune defect.

The role of EBV in the pathogenesis of Burkitt's lymphoma has been suggested, but is unclear. While 90% of patients with the African (endemic) forms carry EBV genomes in their cells, only approximately 15% of patients with the non endemic (sporadic) forms do so, indicating that its function can be substituted by other factors. Many studies are ongoing to understand the role and the timing of EBV infection in the development of lymphoma; the role of EBNA1 (the only latent gene expressed in Burkitt's lymphoma which may be involved in the deregulation of the translocated *c-myc* gene) and its different polymorphic forms; and the manner in which EBV-positive Burkitt's lymphoma escape immunosurveillance.

CLASSIFICATION AND DIAGNOSIS

During the past 20 years, several classifications have been used, several in the U.S.A. (the Rappaport's and the Lukes' classifications followed by the Working Formulating for clinical use) and another in Europe (the Kiel classification). The improvement of immunophenotyping and the development of new antibodies which can be used on paraffin sections has benefited pathological examination and new entities have been described. In 1994, the REAL classification (Revised European American classification of Lymphoïd neoplasms) attempted to standardise classification of lymphoid malignancies and incorporated the newly described entities [1]. Some entities are still described as 'provisional', requiring further definition. A further meeting organised by WHO should complete (or replace?) this classification.

These changes should not impact on the care of children, as virtually all NHL are diffuse and limited to 4 major subtypes; Burkitt's, lymphoblastic, large B-cell and anaplastic Ki1+ large cell lymphomas. The first two groups represent 70–80% of diagnoses.

Burkitt's lymphoma

Burkitt's lymphoma is an aggressive diffuse neoplasm of B-lymphocytes which express surface monoclonal immunoglobulin (slg) and various B-cell differentiation antigens such as CD19, CD20 and CD22. The classical form is characterised by a homogeneous proliferation of medium size cells, having a round nucleus with a coarse chromatin and several prominent nucleoli and a narrow basophilic cytoplasm with lipid vacuoles. When these features are not all present, the term Burkitt's variant is sometimes applied. In other cases, the distinction between Burkitt's and large B-cell lymphoma is difficult as if there was a continuum between these two entities. The 'Burkitt-like' provisional entity of the REAL includes these forms.

Burkitt's lymphoma are characterised by a non random chromosomal translocation involving the proto-oncogene *c-myc* on chromosome 8q24 and one of the heavy μ or light κ or λ chain immunoglobulin constant region genes, either on chromosome 14q32 (the most frequent), 2p12 or 22q11, respectively. Molecular studies have shown different sites of breakpoints, which vary in different parts of the world.

Lymphoblastic lymphoma

These lymphomas are restricted (in the first Kiel classification, it included Burkitt's lymphoma) to those with cell cytology defined as L1 or L2 in the FAB classification. Convolutions of the nucleus are frequent, but not required for the diagnosis. The majority of these lymphomas are derived from

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immature T-cells and express markers of intrathymic T-cell differentiation. A minority (approximately 5%) express a pre-B cytoplasmic μ-chain and common ALL (acute lymphoblastic leukaemia) antigens [HLA-DR+, CD10 (CALLA)+].

Unlike ALL, fewer cytogenetics and molecular studies have been performed due to difficulty in obtaining sufficient tumour material. Normal karyotypes or translocations involving the *TCR* genes on chromosome 7 or 14 have been found. Further studies have to be performed to determine whether there are cytogenetic differences between T-ALL and T-NHL.

Large B-cell lymphoma

Large B-cell lymphoma in children generally corresponds to the type commonly seen in adults and described as centroblastic in the Kiel classification. A special entity is the lymphoma arising in the mediastinum with marked sclerosis.

Anaplastic large cell lymphoma (ALCL)

This particular clinical and histological entity was initially described as 'malignant histiocytosis' because of the presence of very large malignant cells resembling histiocytes. In 1985, Stein re-described this entity as Ki1+ anaplastic large cell lymphoma. They express CD30, an activation antigen, first identified on Reed–Steinberg cells, and recognised by Ki1 or Berh2 antibodies. In the REAL classification, only ALCL with T-cell or indeterminate immunophenotype are included in this category. The precise boundaries with Hodgkin's disease and some peripheral T-cell lymphomas sometimes are not clear.

Translocations involving 2p23 appear specific to ALCL, the most frequent being the t(2;5) (p23;q35), involving the nucleophosmin gene (*NPM*) and a gene coding for a kinase, called Anaplastic Lymphoma Kinase (ALK). The NPM-ALK fusion transcript has been identified. It can now be detected on paraffin sections by ALK antibodies. This should improve the definition and recognition of the ALCL.

TREATMENT

Cure rates of NHL dramatically improved from less than 20 to $\geq$ 70–80% in the past 20 years. Chemotherapy is currently the key to treatment. Surgery is limited to the removal of very localised tumours, especially abdominal lymphoma revealed by intussuception. Radiotherapy is no longer used, except in very rare circumstances. There is evidence that therapy must be adapted to the different subtypes of NHL, especially Burkitt's and the lymphoblastic lymphomas.

Burkitt's lymphoma

This very fast growing disease is characterised by a high proliferation rate and a short cell cycle time. It generally presents with large tumour burden and disseminates early, especially to the CNS. Relapses always occur during the first year of treatment. Hence, therapy has to be intensive, but risk-adapted, to be of short total duration and to include CNS directed therapy. Drug combinations generally given in fractionated doses or in continuous infusion are delivered as 'pulse' courses with short intervals.

There are clinical differences between 'endemic' forms (younger median age, frequent facial involvement and paraplegia) and 'non endemic' forms (predominance of abdominal tumours, frequent bone marrow involvement). However, it is not clear if they correlate with a different prognosis.

The recognised prognostic factors which reflect tumour burden are stage, LDH (lactate dehydrogenase) level, bone marrow or CNS involvement. Response to treatment, such as the response to the prephase in the LMB(?) protocol [2, 3] or complete response after 2 or 3 courses in the LMB [2, 3] and BFM (Berlin-Frankfurt-Munster Group) protocols [4, 5] also appear to be prognostic and should be taken into account when making treatment decisions. Complete resection, which is possible (and meaningful) only in the case of limited disease, is sometimes used to define a group with better prognosis.

In Europe, two cooperative groups contributed to improvement of survival rates, the French Society of Pediatric Oncology (SFOP) with the LMB protocols [2, 3] and the German-Austrian group with the BFM protocols [4, 5].

In the last LMB study, the LMB 89, patients were classified into three prognostic groups receiving treatment of escalating intensity. Three year event-free survival (EFS ± SEM) was 96% ± 4 for 122 stages I and II patients, 93% ± 3 for 280 stages III patients and 88% ± 4 for 62 stage IV and 102 L3 ALL patients. Among stage IV and ALL patients, it was 95% ± 4 (97 patients) and 79% ± 8 (67 patients), respectively, when CNS involvement was absent or present at diagnosis [3].

In the last BFM study, the BFM 90, patients were also classified into three slightly different risk groups, and EFS (± SE) was 95% ± 5 for 49 stage I patients, 98% ± 1 for 114 stage II patients, 86% ± 3 for 171 stage III patients, 83% ± 8 for 23 stage IV patients and 76% ± 8 for 56 B-ALL patients [5].

From these and other successful protocols [6–9], it appears that the 3 most important drugs are cyclophosphamide, high-dose methotrexate (HD-MTX) and cytosine arabinoside (Ara-C). Cyclophosphamide's efficacy is well known since the description of the disease by Burkitt. It is usually given fractionated every 12 hours. Ifosfamide has been introduced in some protocols to alternate with cyclophosphamide, but without evidence of superiority [4, 5]. The combination of Ifosfamide and VP16 which has been shown to be effective in phase II trials has been incorporated into the NCI protocol [6]. Currently, it is under investigation in a randomised study of the Pediatric Oncology Group (POG), U.S.A.

HD MTX is another very important drug because of its demonstrated efficacy in CNS 'prophylaxis' or treatment and its systemic efficacy. High-dose treatment is necessary in advanced stage, as clearly demonstrated in the BFM studies—when MTX was increased from 500 mg/m^2 to 5 g/m^2, EFS of patients with L3 ALL (BFM 86 study) or abdominal stage III with elevated LDH level (BFM 90) increased from 50% to approximately 80% [4, 5]. However, the optimal high-dose and the length of infusion is still questionable. The LMB protocols successfully used 3 g/m^2 in 3 h infusion for CNS prophylaxis and currently is the only protocol to use such a short infusion duration. The BFM 95 study has randomised the duration of MTX infusion, 4 h or 24 h.

Ara-C given fractionated or in continuous infusion is the third most important drug. H-D therapy is probably necessary for higher risk patients with massive bone marrow involvement and CNS disease. H-D-Ara-C in association with VP16 (CYVE course) [10] in the LMB 86 protocol significantly improved the outcome of these patients. This drug combination was part of the BFM 90 protocol (course CC) for patients who responded partially and is now part of the BFM 95 protocol for patients with higher risk factors. Results of this ongoing study will show if it's introduction improves cure rate.

In contrast to bone marrow disease, patients with CNS involvement still have the worst prognosis. Is it because the CNS is a sanctuary or does it reflect more disseminated disease? Whatever the reason, with the association of H-D MTX, H-D-Ara-C, triple intrathecal injections and efficient systemic therapy, cure rates now reach 75% [3]. Intraventricular injections might be more effective than intrathecal injections, and cranial radiotherapy seems of little use [11, 12].

Intensified therapy, adapted to tumour burden, is essential during the first 4 months of treatment. In addition to a patient's already poor condition and/or disease-related metabolic problems, especially acute renal failure and tumour lysis syndrome, treatment toxicity is high. Grade 4 haematological toxicity and severe mucositis are frequently encountered. Therapy-related death rates diminish as the experience of investigators with a given protocol increases. This should be considered by anyone who applies a protocol from another institution or group. Improvements in the management of the tumour lysis syndrome can be made. Urate-oxidase, used for a long time in France and more recently in Italy, degrades uric acid to allantoïne which is highly soluble in urine and prevents urate nephropathy [13]. Hopefully it will be introduced soon in many other countries. Cytokines such as G- or GM-CSF when used with these alkylator-based regimens do not seem to decrease the hospitalisation or infection rates [14].

Longer treatment duration (> 8 months) is not justified. In localised disease, 2 or 3 courses seem sufficient, whilst in advanced disease, the number of courses ranges from 4–8 courses. Long term sequelae (infertility, anthracyline-related cardiomyopathy and second malignancies) justify an attempt to decrease the total dose of alkylating agents and anthracyclines without jeopardising cure rates. This is one of the objectives of the ongoing FAB LMB 96, an international randomised trial with the collaboration of France, the UKCCSG and the CCG of the United States.

What is the role of high-dose chemotherapy with bone marrow or peripheral stem cell rescue? Achievable high cure rates with contemporary chemotherapy do not justify its use in first complete remission. The two recognised indications are first partial remission with documented viable cells in a residual mass (remission failure) or second remission. In relapse, it is difficult to find an effective rescue chemotherapy, but perhaps new drugs will be developed which are effective in this disease [15].

Lymphoblastic lymphomas

Successful treatment programmes for T-cell lymphoblastic lymphomas are derived from protocols designed for therapy of high risk acute lymphoblastic leukaemia, specifically the BFM protocol [4], and the LSA2L2 protocol and its derivatives, with cranial irradition or HDMTX to decrease CNS relapses [16]. Attempts have been made by several groups to improve treatment outcome over 75%. More recently, the BFM group reported an EFS of 92% ± 3 in study 90 [17].

The introduction of HDMTX allowed the reduction of cranial radiation therapy to 12 Gy in BFM study 90. However, the impact of cranial radiation therapy on the control of systemic disease in patients without CNS disease is still controversial. In addition to its role in CNS-directed therapy, there is a rationale for the use of HDMTX in systemic treatment of T-cell lymphomas. HDMTX produces higher intracellular levels of MTX-polyglutamates (the drug's active metabolites) than lower doses.

Weekly repeated high-dose asparaginase (25 000 u/m^2) has improved outcome in both the Dana Farber Cancer Institute studies and POG study 8691/8704 [18]. However, its addition to epipodophyllotoxin-based chemotherapy may potentiate the development of epipodophyllotoxin-associated secondary leukaemia [22].

Should pre-B lymphoblastic lymphomas be treated as T-lymphoblastic lymphomas? Treatment could probably be less intensive especially in low stage disease, but because the number of cases is small, they are generally treated according to the same protocol.

Large cell lymphomas

Ki1 positive large cell anaplastic lymphoma is a rare disease. Large series accrue approximately 10 patients per year. Should they be treated with the same protocols as the other large cell lymphomas and not considered a special entity as is the case in the United States [21]? Or should they be considered as a specific entity as is the case in Europe? Overall survival rates are around 70–80% whatever the 'B-cell-like' [19, 20] or 'T-cell like' protocol. However, EFS is often lower, indicating that relapses can be rescued. In several studies it appeared that cutaneous and mediastinal (or lung) involvement were indicators of poor prognosis [19, 20]. To answer these questions about therapy and prognostic factors, large international cooperative studies are warranted.

Other large cell lymphomas are of B-cell phenotype. In Europe they are enrolled on the same protocol as Burkitt's lymphoma with similar outcome. However, late relapses occur after more than a year from diagnosis.

Localised NHL

These require less intensive therapy than advanced stage lymphomas and CNS directed therapy can be avoided in B-cell stage I and abdominal stage II. In some programmes, localised NHL are treated with the same protocol whatever the histology. However, EFS is worse in lymphoblastic diseases when treated with short and pulse treatment [23]. This supports the attitude of those in the SFOP and BFM, in whose studies treatment is adapted to histology and immunophenotype as in advanced stages.

NHL in immunocompromised patients

In contrast to AIDS patients where risk- (patient and lymphoma-related) and histology-adapted chemotherapy is essential, transplant-related NHLs often respond to withdrawal of immunosupression and/or addition of acyclovir, interferon and monoclonal antibodies. However, the optimal therapy for AIDS patients with large cell NHL, or those with progressive NHL post transplantation is still to be defined. Collaborative multicentre prospective studies are warranted in these rare NHL to address the epidemiology, biology and therapeutic questions.

CONCLUSION

Over the past two decades, NHL has become a curable disease. This progress is the result of understanding the heterogeneity of this group of diseases and of the use of histology- and risk-adapted therapy in the context of large prospective multicentre trials. Therapeutic refinement of the role of

radiation therapy, surgery and bone marrow transplantation have been made. However, current challenges include diminishing therapy-related morbidity and late effects and improving patients' quality of life. Advances in molecular biology, surveillance of minimal disease and novel chemotherapeutic agents may further improve the cure rates.

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Commentary

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As one of the lead investigators with the French LMB Group, Dr Patte has been involved in setting the pace for improving outcome in Burkitt's lymphoma over several years. In her useful overview she has highlighted the key areas in childhood NHL where progress has been made and those where there are still further challenges.

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Despite Burkitt's lymphoma being one of the first cancers in which clearly defined molecular mechanisms have been identified, causal mechanisms are still speculative. The recent upsurge of interest in the role of Epstein–Barr virus associated with lymphoproliferative disorders (LPD) in transplant recipients and AIDS patients will undoubtedly shed further light on this subject. With the increase in number of solid organ transplant procedures being done in children and the