Childhood non-Hodgkin's lymphoma: recent advances

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Introduction

Non-Hodgkin's lymphomas (NHL) occur much less frequently in childhood than in adulthood. The histological subtypes are also restricted to some entities. The more frequent include Burkitt's lymphoma (BL) (about 50–60% of cases), followed by the lymphoblastic lymphoma (LBL) (25–35%), the diffuse large B-cell lymphoma (DLBL) (8–12%), and the anaplastic large cell lymphoma (ALCL) (8–12%). The proportion depends mainly on the geographical origin of the patients and the upper limit of the age, DLBL being more frequent in adolescents. Although the proportion of these different subtypes is lower in adults, their absolute number might not be very different from that in children.

Due to the predominance of extranodal primary sites, the usual staging classification in children is St. Jude's classification (Table 1), which is different from the Ann Arbor classification used in adult NHL.

Many advances have been made in childhood NHL, thanks to co-operative national studies with cure rates higher than 70%. Some of these studies might be of benefit in the treatment of adult NHL.

The lessons learned from the large co-operative trials can be summarised as follows.

Burkitt's NHL

Generalities

Burkitt's NHL arises preferentially in the abdomen and particularly on the gut in the ileocaecal region, and regionally with ascitis and involvement of other intra-abdominal viscera. Other sites of the disease are mainly in the head and neck (Waldeyer ring, maxillaries, orbit, thyroid, cervical node), but also in the kidney, other nodes, and bone. The disease spreads rapidly, regionally and at a distance, especially in the bone marrow and the central nervous system (CNS). Burkitt's leukaemia, called L3 ALL, is rare. Burkitt's NHL and L3ALL are different faces of a similar disease characterised by malignant cells having the same morphology, the same immunological profile, and the same specific cytogenetic abnormalities. Although it does not correspond to clinical presentations, the arbitrary border between NHL and ALL is 25% blasts (or 30% in the adults) in bone marrow.

Another characteristic of Burkitt's disease is the high proliferation rate and the short doubling time, with the majority of the cells being entered in the cell cycle. Tumours are generally huge at time of diagnosis. One major preoccupation is the "tumour lysis syndrome" (TLS), occurring spontaneously and

Table 1
St. Jude's staging for childhood NHL

Stage	Description
Stage I	A single tumour (extranodal) or single anatomical area (nodal) with the exclusion of the mediastinum or abdomen.
Stage II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tract tumour, usually in the ileocoecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected.
Stage III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All the primary intrathoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease, unresectable. All paraspinal or epidural tumours, regardless of other tumour site(s).
Stage IV	Any of the above with initial CNS and/or bone marrow involvement.

precipitated at the start of the treatment. It must be prevented or treated by intensive hyperhydration and uricolylic. Urate oxidase transforms uric acid into allantoin which is much more soluble in urine and does not precipitate in the kidney as uric acid does, causing urate nephropathy and renal deficiency [1,2].

There is no advantage in performing major tumour resection or debulking procedures. Extensive surgery is unnecessary and followed by tumour regrowth. It delays and may complicate chemotherapy.

Radiotherapy is no longer used. It gives no advantage over chemotherapy and adds both immediate and long-term toxicity to the treatment. This was demonstrated in randomised studies, first in advanced stage diseases [2,3], then in localised diseases [2,4] (in [4], all localised stages with any histology were included, and the conclusion of no advantage of local radiotherapy applies to all histologies).

In twenty years, the cure rate of advanced stage Burkitt's disease has changed completely. In the mid-1970s, only about 10% of children with the disease could be cured, with the majority dying in a few weeks. Twenty years later, 90% of the children are cured. This considerable improvement was achieved through national prospective studies, only a few being randomised, and without new drugs. The 3 groups who mostly contributed to the improvement of the cure rate are the SFOP (Société Française d'Oncologie Pédiatrique; France), the BFM (Berlin–Frankfurt–Münster; Germany–Austria), and the POG (Pediatric Oncology Group; USA).

LMB studies

Since 1981, the SFOP has developed a specific strategy for B-cell NHL, the first three have been decided for advanced stage Burkitt's disease [5,6]. The general scheme was the following: a prephase called COP, with low doses of cyclophosphamide (CPM), vincristine (VCR) and prednisone, is followed by 2 intensive induction courses called COPADM, based on high dose methotrexate (HD MTX) and CPM in addition to VCR, prednisone, doxorubicin, and 2 consolidation courses based on Ara-C as continuous infusions. The different LMB studies are detailed to show how progress was made from one study to another. Noteworthy was that relapses were not delayed with a more intensive treatment, still occurring within the first year.

The first study, LMB81 (1981–1984) [5], a one-year intensive 9-drug chemotherapy regimen, which included 114 patients, succeeded in increasing the survival rate of 93 patients with stages III and IV lymphoma and ALL, without central nervous system (CNS) involvement, to 75%. Only 1% of isolated CNS relapses occurred with CNS-directed treatment based on high-dose methotrexate (HD MTX: 3 g/m^2 in a 3 h infusion) and intra-thecal injections of MTX. However, toxicity-related mortality was high (10%). Two prognostic factors were identified as predictive of outcome: CNS involvement (21 patients, event-free survival (EFS) ($\pm$ SD 19% $\pm$16) (EFS, event being: tumour progression or relapse, secondary malignancy, death from any cause, i.e., tumour, treatment-related toxicity or non-treatment-related death)) and the absence of complete remission after 3 multi-agent chemotherapy courses.

The second study, LMB84 (1984–1987) [5], a randomised trial comparing 2 lengths of treatment, 3 months versus 7 months, demonstrated the efficacy of a short treatment for patients without CNS involvement (CNS−). It also showed that: (1) patients who achieved a partial remission (with documented viable cells in the residual mass) after 3 chemotherapy courses could be salvaged with high-dose chemotherapy (HDCT) and autologous bone marrow transplantation (ABMT) [7]; (2) patients whose tumours did not respond to the prephase, i.e. the first week of treatment, ultimately failed (21 patients, EFS = 22% $\pm$20); and (3) toxicity-related morbidity declined as investigators gained experience with the protocol, even though the induction phase remained unchanged.

During the same period (1985–1989), the pilot LMB86 study was conducted for patients with CNS disease (CNS+) or L3ALL with more than 70% of blasts in bone marrow (patients who appeared at a higher risk of CNS disease in our previous experience [8]). Treatment of CNS disease was intensified with a higher dose of MTX (8 g/m^2 in a 4 h infusion) in the induction phase, high-dose cytarabine (HDAra-C) and VP16 during the consolidation phase (this association called CYVE course was previously tested with success in relapse) [9], and cranial irradiation. The EFS of these patients increased dramatically to 75% $\pm$9 (24 CNS+) and 82% $\pm$12 (11 ALL CNS−).

Based on these results, a new protocol was designed for all consecutive patients with B-cell lymphoma including the large B-cell type, whatever the stage, low stages included. The aims of the study were: to confirm the results of previous studies, especially LMB86 findings; to see whether a treatment strategy adapted to the tumour burden and to the initial tumour response to chemotherapy would maintain a good or improve a worse outcome; and to identify the remaining or any new prognostic factors [10]. Patients were stratified into 3 therapeutic groups based on initial resection (localised tumour), stage, CNS involvement (group A: low risk = re-

sected stage I and II; group B: intermediate risk = patients not included in group A or C; group C: high risk patients = initial CNS involvement and/or bone marrow involvement with more than 70% blasts). Treatment was further intensified for patients who did not respond to COP and for patients with residual viable cells after the consolidation phase.

The 5-year survival and EFS of the 561 enrolled patients is 92.5% (95% CI, 90–94) and 91% (89–93), respectively. EFS is 98% for stage I + II, 91% for stage III, and 87% for stage IV and B-ALL. Among stage III patients, EFS was 89.5% for patients with lactate dehydrogenase (LDH) level > two-fold the normal value (N×2) vs. 95% for LDH ≤ N×2. Among stages IV and L3ALL, CNS involvement was the only prognostic factor (79% for CNS+ vs. 92.5% for CNS−). The EFS of the 100 patients with L3ALL was 88%, and 92% and 83% for patients without and with CNS ($n = 35$) involvement, respectively.

The following study, the FAB LMB96 (May 1996–June 2001), was a randomised international trial with the participation of SFOP, UKCCSG (United Kingdom Children's Cancer Study Group) from Great Britain, and CCG (Children's Cancer Group) from the USA. It was an attempt to further reduce total drug dosage, especially that of cyclophosphamide to avoid sterility in boys, to reduce treatment duration, and to suppress cranial irradiation in patients with initial CNS involvement. More than 1100 patients were included. This large series will provide not only therapeutic results, but also information on epidemiology, histology, cytogenetics of B-cell NHL in children and adolescents and on some subgroups of patients (adolescents, mediastinal NHL, etc.). First therapeutic results were presented at the American Society of Clinical Oncologists (ASCO) meeting in June 2003 and can be summarised as follows. Excellent results of LMB89 group A, with only one month's treatment, were reproduced on a large number of low risk patients [11]. In the intermediate risk group, treatment can be reduced to only 4 courses instead of 5, and cyclophosphamide total dose to 3.3 g/m^2 instead of 5.3 g/m^2, but treatment intensity during the first month of treatment is a major prognostic factor [12]. In the high risk group, attempt to reduce treatment was a failure [13]. This result also confirms the impact of early treatment intensity.

BFM protocols

B-BFM strategy is based on 2 alternating five-day courses including dexamethasone, intermediate dose or HD MTX in 24 h infusion, intrathecal injections in each course and ifosfamide/cytarabine/epipodophylline or CPM/doxorubicin in alternate. In the course of the first four consecutive BFM studies (numbered BFM-81, 83, 86, 90) [14,15], treatment intensity was progressively increased, treatment duration reduced and CNS irradiation withdrawn. In the BFM 90 study (1990–1995) [15], patients were stratified into 3 risk groups, a little different from the SFOP stratification, based on resection, site, stage and LDH level and received 2, 4 or 6 courses. The insertion of an Omaya reservoir was recommended for patients with CNS involvement in order to deliver MTX and Ara-C intraventricularly. The 6-year EFS of the 413 patients was 89%. It was 97%, 98%, 88%, 73% and 74% for stage I, II, III , IV and B-ALL NHL, respectively [15].

The most remarkable data is the increase of EFS from about 50% to about 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 g/m^2 to 5 g/m^2.

In the BFM 95 study, in which the patients were stratified into 4 therapeutic groups, the duration of the MTX infusion was randomised (24 h versus 4 h). Final results are not yet published, but the final analysis is in favour of the 24 h infusion in the higher risk patients, whereas short duration infusion is as efficient as long duration in lower risk patients with less toxicity [16].

The other protocols

The others major contributions will not be detailed. The POG (Pediatric Oncology Group, of the USA) ran the POG 8617 randomised study which included 277 patients with advanced stage disease, but without CNS involvement [17]. The study did not show the benefit of adding a course of ifosfamide/VP16 to the "Total-B Therapy" including CPM, doxorubicin, prednisone, HD MTX and HD Ara-C. The National Cancer Institute (NCI) published a unicentric series of 75 children and adults with B-cell disease of any stage [18]. EFS was 89% and was similar in adults and children, in Burkitt's and large-cell NHL. The Instituto di Tumori in Milan published interesting results in a very small unicentric series of 29 patients with advanced stage with a very short treatment duration [19].

Treatment recommendations

It is now accepted that Burkitt's NHL must be treated with an intensive pulse polychemotherapy regimen, with the shortest intervals between courses. Treatment duration is short, a few months, all the relapses occurring during the first year. It must also

be adapted to the extent of the disease. The main 3 drugs are: CPM, HD MTX and Ara-C (HD in advanced stages). Other efficient drugs are corticosteroids, VCR, doxorubicin, ifosfamide, VP16. CNS prophylaxis is essential.

The SFOP studies indicated that response to treatment is important and should somehow be taken into account, and that early treatment dose intensity is essential.

Burkitt's NHL in adolescents

As in those with other types of tumours, adolescents with NHL are treated either in the paediatric department with paediatric protocols or in the adult department where they are diversely treated according to a paediatric or an adult protocol, but often without registration in a study. Information concerning 15–20-year-old patients is limited and contradictory. We have already mentioned the small NCI series with similar results in patients under or over 18 years of age [18]. In the SFOP LMB89 study, patients aged > 15 years had a worse EFS than the younger patients [10], but the number of patients was small and overall survival rates were not different. In the FAB LMB96, there was no significant differences between patients younger or older than 15 years after adjustment for histology. Recently, the BFM group looked at the outcome of their patients > 15 years of age, and found a significantly worse outcome for the patients with Burkitt's, but not for the patients with other histologies.

An epidemiological study is going on in France to find out more about adolescents: where are they treated? with which treatment? with which results? Are they registered in studies or trials?

Burkitt's NHL in adults

Until recently, results of treatment in adults with Burkitt's was poor, especially in advanced stages. When "paediatric" regimens were tried, the results improved. Now, paediatric protocols, such as the SFOP LMB [20] and the BFM [21], have been tested and "adapted" (generally by reducing dose of HD MTX) to treat adult Burkitt's NHL. Treatment results were much improved, although not identical to children's results. The reasons for this difference are not yet completely clear, although the following suggestions can be made: (1) The biology of Burkitt's NHL is not the same in children and adults, as suggested by 2 observations. From the pathologist's point of view, Burkitt's NHL in adults appears more heterogeneous than in children with a higher frequency of atypical forms; in the protocol LMBA 95 for adults, the percentage of non-responders after COP (patients with worse prognosis) is higher than in the paediatric LMB89 series. More biological studies including children and adult tumours have to be performed to confirm that these observations reflect different biologies. (2) Adults do not tolerate HD MTX as well as children do and, generally, the dose of this drug is lowered in adult protocols. Knowing that the BFM group demonstrated the impact of the dose of HD MTX on survival, the decrease of the dose of MTX might explain the difference. (3) The FAB LMB 96 demonstrated the necessity of the dose intensity during the first weeks of treatment. Is dose intensity similar in children and adults? Are the intervals between the courses as short as possible?

Targeted therapy with the anti-CD20 monoclonal antibodies

There are anecdotal observations showing efficacy of rituximab in Burkitt's NHL, but there is no study clearly demonstrating efficacy and/or benefit for rituximab in Burkitt's disease. Although some have already decided to include rituximab in their treatment for adults, the impact of this targeted therapy needs to be demonstrated in phase II and randomised studies, as well in the adulthood or childhood settings.

Diffuse large B-cell NHL

The SFOP and the BFM groups treat DLBL patients with the same protocols as Burkitt's, with similar results to those obtained in Burkitt's. In the LMB 89 study, the outcome of the 420 patients with Burkitt's lymphoma and that of the 63 with large B-cell lymphoma were similar, with an EFS of 92% and 89%, respectively [10]. We reclassified these 63 patients according to the Ann Arbor classification and to the IPI, but did not find any differences either. Here again, it is not clear if the better results obtained in children are due to the therapy used or to different biology (or both).

In a randomised study, the POG showed the benefit of HD MTX and HD Ara-C in combination with the APO (doxorubicin, prednisone, vincristine) regimen [22].

Lymphoblastic lymphoma

Treatment must be intensive, but semi-continuous and prolonged (18–24 months), more similar to treat-

ment of high-risk leukaemias. Most of these lymphomas are of the T-lineage, but a few are of the B-lineage. Although their biology is not similar, they are generally treated with the same protocols.

Two protocols are recognised as giving the best results in lymphoblastic NHL: the LSA2L2 and the non-B-BFM ones.

The LSA2L2 and derived protocols

In 1979, the study results of the LSA2L2 protocol given to 39 patients were published. The protocol was then integrated into randomised studies by the CCSG [23] and the POG in the USA. It consisted of a two- or three-year 10-drug intensive regimen administration. After the 5-week induction, drugs were given for five days a week during consolidation and every two weeks during maintenance. With CNS prophylaxis based on IT MTX, isolated CNS relapse rate was 8–15%.

Some tried to improve CNS prophylaxis by the addition of cranial irradiation or HD MTX. At the Institut Gustave Roussy in France, the original protocol was modified by the addition of 10 HD MTX (3 g/m^2 in 3 h infusion) [24]. The EFS was 79% for 33 stage III patients and 72% for 43 stage IV patients (24 of whom had more than 25% bone marrow involvement). Only one isolated CNS relapse occurred among the 69 patients without CNS involvement.

However, this protocol seemed complicated with results that were slightly inferior to those of BFM, which is now the reference.

BFM and derived protocols

Since 1976, non-B type lymphomas have been treated using the same protocol as that used for acute lymphoblastic leukaemia. The induction (protocol I: Pred, VCR, daunorubicin, L-Asparaginase followed by CPM, Ara-C, 6-MP and associated with MTX IT) and the reinduction (protocol II: same drugs, but lower total doses and dexamethasone replacing Pred) underwent very few modifications during studies 76, 81, 83, 86, and 90 [25]. These phases are followed by a maintenance with daily 6-MP and weekly MTX. Four courses of ID MTX (0.5 g/m^2) were introduced in study 83, and replaced by HD MTX (5 g/m^2 in 24 h infusion) in study 86. In parallel, preventive cranial irradiation was reduced from 18 Gy to 12 Gy. Since 1976, results have been about the same: EFS was 78% for 42 stage III and IV patients treated in study 76, and 79% for 71 patients treated in study 86 [14]. However, in study 90 which enrolled 101 patients, EFS improved to 90% without significant change in the chemotherapy regimen [25]. This might be due to the long experience of the investigators with the protocol. In the ongoing BFM 95 study, cranial irradiation was deleted in CNS-patients. Results are not yet known.

Several European groups and centres which have adopted the BFM protocol or slightly modified protocols for treatment of leukaemia now use the same protocol for lymphoblastic lymphoma.

Other studies

Other studies used other regimens, which are "leukaemia-like" protocols or protocols common for T-lymphoblastic NHL and ALL. One such randomised POG study demonstrated the importance of asparaginase in these diseases [26] and another investigated the benefit of HD MTX (the interim analysis was in favour of it). A CCG study is also investigating the benefit of HD MTX compared with intensified intrathecal injections.

Summary

With intensive "leukaemia-like" protocols, EFS of lymphoblastic NHL is between 75% and 90%. Randomised studies have demonstrated the efficacy of HD MTX and asparaginase. The other efficient drugs are corticosteroids, doxorubicin or daunorubicin, cyclophosphamide, Ara-C, methotrexate, 6-mercaptopurine, VP16.

Presently, the best results are obtained by the non-B-BFM regimen with an EFS between 80% and 90%. So far, no prognostic factors have been identified.

In the near future, an international European study will start, investigating in a randomised trial the benefit of dexamethasone compared with prednisone and the duration of treatment (18 months vs. 24 months). It will also focus on the search for prognostic factors (biology, early tumour response).

In childhood lymphoblastic NHL, considering the overall good outcome and in the ignorance of prognostic factors, there is no place for high-dose chemotherapy with stem cell rescue in first complete response (CR). This attitude seems recommended in adulthood lymphoblastic NHL [27], but with a regimen quite different from those recommended in children. Although older patients might not tolerate similar treatments, the question is raised as to whether to treat younger adults according to "paediatric" regimens, as was suggested for leukaemia in a recent French analysis [28].

Anaplastic large cell lymphoma

This disease is rare in children as well as in adults. In adults, it is recognised to have a better outcome than the other peripheral T-cell lymphomas.

A specific translocation t(2;5) (or variants) is found in most cases and its fusion protein is now detectable on paraffin sections by the ALK-1 antibody. Most of the cases are ALK-1-positive in children, which is not the case in adults where the ALK-1-negative cases seem to have a worse outcome.

There are still many questions on the best treatment scheme for this disease and the treatment duration. The review of 3 series of children treated according to "B-like" protocols (SFOP [29], BFM [30], UKCCSG [31]) allowed the identification of bad prognosis factors: the mediastinal involvement, the cutaneous involvement and the visceral (spleen, hepatic and lung) involvement [32]. These factors are used to stratify the patients in the current European randomised study, which is asking a question on the best modalities of HD MTX administration and on the benefit of weekly treatment with vinblastine during one year in the advanced stages. The treatment backbone is a B-BFM scheme which gave similar results to other schemes, but with lower cumulative doses of alkylating agents and of anthracyclines [30].

In the already cited POG randomised study for large cell lymphoma, contrary to what was found for LBCL, the addition of HD MTX and Ara-C to the APO regimen was not found to be beneficial for ALCL [22].

Conclusions

In the 4 subtypes of NHL observed in children, multi-centre national studies led to substantial improvement in the cure rates, with an overall probability of cure of at least 75%.

The 2 major subtypes seen in children, Burkitt's and lymphoblastic, represent a low percentage of the NHL seen in adults, although the absolute numbers might not be so different. These aggressive NHL now have a good outcome in children, with treatment almost exclusively being with chemotherapy, including the necessary CNS prophylaxis. When the paediatric therapeutic schemes are used in these NHL in adults, although modified to improve tolerance, significant survival improvement was generally observed, but not as high as that observed in children [21,33]. These different results are also seen in DLCL which represents a minority of NHL in children, but whose frequency increases during adolescence. It is not yet known if the differences in outcome are due to treatment modifications or application (as showed in studies done in ALL in adolescents) [28] or to differences in tumour biology, or both.

Paediatricians and adult haematologists should work more closely on NHL of the same ypes, in the therapeutic as well as the biological fields. The promising new biological techniques, such as DNA or tissue arrays, comparing tumours of the same histology, but occurring in patients of different ages, should give some answers to the pressing questions.

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