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European School of Oncology: Management of Non-Hodgkin's Lymphomas: Conclusions of the European School of Oncology Meeting, 1986

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On 15 December 1986 in Strasbourg (France) the first Intercities Meeting of the European School of Oncology was held with a survey of the current status of non-Hodgkin's lymphoma (NHL) management. The conclusions of this meeting are presented here. The Working Formulation for clinical use [1] (Table 1) is used throughout this paper.

I. FOLLICULAR LOW GRADE NHL

These lymphomas are characterized by the presence of a follicular pattern of infiltration of small cleaved cells or small and large cells. The percentage of large cells required to define low grade NHL is still a matter of controversy [2]. The course is characterized by three phases: the first is marked by noticeable lymphadenopathies which do not seem to change with time; in the second phase they expand rapidly and symptoms can appear; in the third phase there is transformation of the low grade NHL into a high grade type resistant to therapy. The duration of each phase varies considerably from patient to patient. The major problems associated with these NHL are the low frequency of truly localized forms, the impossibility of curing a large number of patients, the difficulty of obtaining a true complete remission (CR), and a constant mortality rate with a median survival of 6–8 years. Low survival is associated with such variables as age, bulky tumor, B symptoms (fever, sweats and weight loss) and increased lactate dehydrogenase (LDH) level [3]. Recently the percentage of small non-cleaved cells and large non-cleaved cells at diagnosis has been negatively associated with survival and positively with histologic progression [2].

Table 1. Working formulation of histologic types of non-Hodgkin's lymphomas [1]

Low grade		
	A.	ML small lymphocytic
	B.	ML follicular predominantly small cleaved cell
	C.	ML follicular mixed, small cleaved and large cell
Intermediate grade		
	D.	ML follicular predominantly large cell
	E.	ML diffuse small cleaved cell
	F.	ML diffuse mixed, small and large cell
	G.	ML diffuse large cell
High grade		
	H.	ML large cell, immunoblastic
	I.	ML lymphoblastic
	J.	ML small noncleaved cell
Miscellaneous		
	ML composite	
	ML histiocytic	
	ML unclassifiable	

ML: malignant lymphoma.

Localized low-grade NHL can be cured by involved-field radiotherapy [3] and this treatment should be applied to all such patients. Advanced low-grade NHL remains a therapeutic challenge; the patients respond well at first to several regimens but continue to relapse and die. No significant difference between the various treatments have been documented in several randomized trials [4, 5]; single drugs such as cyclophosphamide or chlorambucil produce the

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same results as polychemotherapy (CVP) with or without adriamycin. Some controversy persists as to whether achieving CR has any influence on survival.

Current recommendations for the treatment of these patients are difficult to point out. Some research groups advocate the 'watch and wait' approach till progression [4], while others suggest that intensive chemotherapy should be attempted in some patients [6]. The optimal treatment is not known and should be sought by means of large cooperative trials wherein the widened recruitment could substantially reduce the time needed to obtain meaningful results. Questions which future studies should try to answer are: (a) Is there a group of patients in whom treatment could be delayed till progression? Would the absence of treatment be detrimental in terms of survival or percentage of patients who subsequently undergo histologic progression? (b) Is the dose–response relationship which has been demonstrated in aggressive NHL also applicable to low grade NHL? If so, what is(are) the best regimen(s)? (c) What role, if any, can be played by the new strategies such as interferon or intensification with bone marrow rescue? All of these questions are unanswered, the problem is to define how each particular type of case should be managed.

II. PEDIATRIC LYMPHOMAS

Childhood NHL differ considerably from adult forms in that low and intermediate grade NHL are rare in children; more than 90% of patients have lymphoblastic or small non-cleaved cell types, mostly Burkitt's. Nearly all young patients have widespread disease at time of diagnosis. In lymphoblastic lymphomas malignant cells are small often convoluted immature cells, usually of immature T-cell phenotype not very different from those observed in T-cell acute lymphoblastic leukemia. Intensive combination chemotherapy (Table 2) has totally transformed their prognosis: a regimen such as the LSA_2–L_2 protocol can achieve a long term disease-free survival rate of around 75% in disseminated disease [7].

Non-lymphoblastic lymphomas are of B-cell phenotype and are generally comprised of small non-cleaved cells, of Burkitt's or non-Burkitt's type. The disease generally originates in the gastrointestinal tract, abdominal cavity or Waldeyer's ring. Here too, intensive chemotherapy regimens have changed the prognosis: regimens such as the French LMB protocol [8] or the German BFM protocol [9] can produce a long term survival rate of 60–70% for disseminated disease. For the rare localized NHL, a long term survival rate of 90% has been obtained with less intensive regimens.

Problems persist for the most aggressive presentations: patients with initial CNS involvement, especially when combined with marrow involvement, and those with extensive visceral involvement. Such patients fail to respond to intensive initial therapy. In cases with CNS involvement, high-dose methotrexate with folinic acid rescue or high-dose cytarabine permit some improvement [8]. In the remaining cases, intensification with bone marrow rescue offers some chance of long term survival [10].

III. AGGRESSIVE LYMPHOMAS

Major progress in the treatment of patients with aggressive NHL (intermediate and high grade) has been accomplished since 1975. The addition of adriamycin to the CVP regimen (cyclophosphamide, vincristine and prednisone), resulting in combinations such as the CHOP and BACOP regimens, has led to an improvement in CR rates, with a plateau in the survival curves. This suggests that long term disease-free survival, and perhaps cure, is attainable [11]. The South West Oncology Group has recently reported a more than 10 year follow-up of patients treated by CHOP, indicating that 30% of the patients were probably cured [12].

These results have been dramatically improved by intensive combination chemotherapy (Table 2). Regimens such as M-BACOD [13], ProMACE-MOPP [14], MACOP-B [15], and LNH-80 [16] have been associated with 60–80% CR rates. The increase in CR rates is associated with a decrease in relapse rate, and thus 50–70% of patients survived 3 years or longer. However, long term results (5 or 10 years of follow-up) are not available for all these intensive regimens, and thus the advantage in terms of survival is not definitively known. A major difficulty in comparing these treatments is that they differ with respect to eligibility criteria (prior therapy, stage, performance status, morphological subtypes) and the incidence of known prognostic factors. For example, the M/m-BACOD study clearly demonstrates the importance of performance status, tumor bulk and the number of extranodal sites of disease [17]; but marrow involvement was present in only 10% of cases instead of 25–30% in major studies. The influence of age on response and survival is also well documented [18], but the median age and the number of patients over 60 years differ from one study to the other. A prognostic index was constructed by Shipp *et al.* [17] based on performance status, the diameter of the largest mass and the number of extranodal sites of disease, which divided the patients into three groups with predicted 5-year survival rates of 68, 55 and 24%, respectively. In the LNH-80 regimen we also found these variables to be significant but marrow involvement proved to be the major prognostic factor, both in terms of response and survival. By applying the

Table 2. Drugs included in intensive chemotherapy regimens utilized in the treatment of non-Hodgkin's lymphomas and cited in the text

LSA_2-L_2 [7]:	induction:	CPM, VCR, MTX, DNR, Pred
	consolidation:	AraC, TG, Asp, MTX, BCNU
	maintenance:	TG, CPM, HU, DNR, MTX, BCNU, AraC, VCR
LMB [8]:	induction:	CPM, VCR, Pred, MTX, ADR, AraC, ASP, CCNU, TG
	maintenance:	MTX, CPM, Pred, ADR, CCNU, AraC, TG, Asp
BFM [9]:	induction:	Pred, VCR, DNR, Asp
	consolidation:	CPM, AraC, MTX, MP
	maintenance:	MP, MTX, VCR, Pred
M-BACOD [13]:		Bleo, ADR, CPM, VCR, Dex
ProMACE-MOPP [14]:		CPM, ADR, VP16, Pred, NH_2, VCR, PCZ, MTX
MACOP-B [15]:		MTX, ADR, CPM, VCR, Bleo, Pred
LNH-80 [16]:	induction:	CPM, ADR, VCR, Bleo, mPred, MTX
	consolidation:	AraC, MTX, Asp
	intensification:	CPM, VM, Bleo, AraC, mPred
LNH-84:	induction:	CPM, ADR, VDS, Bleo, mPred, MTX
	consolidation:	AraC, MTX, Asp, VP16, IFM
	intensification:	CPM, VM, Bleo, AraC, mPred

ADR: doxorubicin, Asp: L-asparaginase, AraC: cytarabine, BCNU: carmustine, Bléo: bleomycin, CCNU: lomustine, CPM: cyclophophamide, Dex: dexamethasone, DNR: daunorubicin, HU: hydroxyurea, IFM: ifosfamide, MP: mercaptopurine, mPred: methylprednisolone, MTX: methotrexate, NH_2: mechlorethamine, PCZ: procarbazine, Pred: prednisone, TG: thioguanine, VCR: vincristine, VDS: vindesine, VM: teniposide, VP16: etoposide.

Shipp's index, we obtained 5-year survival rates of 77, 73 and 52%, respectively [19]. Multicenter randomized studies are currently in progress in the US and Europe to define the best therapeutic regimen.

Some issues are still a matter of debate. (a) Should lymphoblasic NHL and small non-cleaved cell NHL in adults be treated like other aggressive NHL? The answer is that true lymphoblastic T-cell NHL in the young adult is similar to T-cell acute lymphoblastic leukemia, especially if the marrow is involved, and should therefore be treated as T-cell acute lymphoblastic leukemia. Non-convoluted non-Burkitt lymphoblastic NHL, as defined by the Kiel classification, are mostly unclassified NHL and should be treated as adult aggressive NHL. Small non-cleaved cell NHL of Burkitt's or non-Burkitt's type are very aggressive NHL in the adult and require intensive regimens such as LNH-80 or intensive pediatric regimens. (b) What duration of chemotherapy is needed? The MACOP-B regimen clearly demonstrates that chemotherapy could be limited if it is intensive. We are currently testing the need for a final intensification in the LNH-84 protocol, in a multicenter randomized study based on the LNH-80 regimen. Preliminary results based on the first 600 patients will be published soon. (c) Are peripheral T-cell NHL (PTCL) different from other aggressive NHL? This question has rarely been addressed, possibly because PTCL were rarely recognized in the past and hence few such patients were included in protocols. PTCL do not readily fit in our present morphological classifications and thus are frequently assigned to the unclassified group or are not diagnosed as NHL but as related disease such as angioimmunoblastic lymphadenopathy [20] or Hodgkin's disease. PTCL patients had the worst prognosis out of all the groups studied in our LNH-80 protocol [19]: median survival was only 14 months for PTCL and not reached for B-cell NHL or untyped NHL. This poor prognosis is related to either death during the induction chemotherapy, failure to respond or early relapses. However in a non-randomized study of 50 PTCL patients, the LNH-80 regimen yielded the best survival figure [21]. (d) What is the place, if any, of radiotherapy in aggressive NHL? Clearly aggressive NHL are not a localized disease, even in cases with a localized presentation. Previous radiotherapy protocols for stages I or II patients have shown that relapses do not occur at the initial site of the disease [22]. Adjuvant chemotherapy after radiotherapy was proven to be indispensable. Results obtained using chemotherapy alone were found as good as those obtained with the chemotherapy–radiotherapy combination [23]. Radiotherapy may

remain useful for CNS localizations or as adjuvant therapy in bulky tumors, although this is debatable.

IV. SALVAGE THERAPY

Twenty to 30% of the patients with an aggressive NHL failed to respond to chemotherapy and 20–30% of those who did respond relapsed. Thus 30–40% of the patients need salvage therapy. No satisfactory universal chemotherapy is widely accepted and no standard recommendation exists for salvage therapy. The problem is that because of the acquired multidrug resistance, patients who fail to respond to initial chemotherapy rarely respond to other treatments. Two solutions have been proposed: alternative regimens with non-cross-resistant drugs, or increased dosage of the drugs. Several alternative regimens have been described during the last 5 years, but very few display the characteristics of a good salvage regimen such as a CR rate of 50%; a relapse rate of less than 20%; no major toxicity, and at least 40% of patients still alive at least 2 years after salvage. The most effective regimen employed ifosfamide, etoposide, methylgag and methotrexate [24] but did not meet these criteria: only 20% of the patients were alive 2 years post salvage. Mitoxantrone may have a crucial part to play in this aspect of lymphoma treatment [25].

Increased drug dosage is feasible if followed by rescue by autologous bone marrow reinjection (ABMR). ABMR has been tested with some success in pediatric and adult patients [10, 26]. CR was obtained in 40% of the patients, with half of them relapsing during the first year, resulting in a less than 25% 2 year survival. Several problems still prevent complete assessment of the merits of this type of therapy. (a) The inability to obtain complete responses in the majority of patients with refractory NHL is the major factor limiting successful ABMR treatment. (b) The possible reinfusion of lymphoma cells is not a real problem, even with unpurged marrow, as indicated by the similar results obtained by the Seattle group with syngenic, allogenic or autologous bone marrow cells. (c) The nature of the ablative chemotherapy or radio-chemotherapy before marrow rescue needs to be stated precisely. One possible alternative would be to perform early consolidation with ABMR in high risk patients at the first CR. This possibility will be tested in our LNH-87 protocol.

The past decade has witnessed major progress in the treatment of NHL with more and more patients surviving at least 5 years who are possibly cured. But considerable work is necessary in order to attain a cure rate of at least 75%. The hardest part remains to be worked out and the challenge of the future can only be met by initiating large prospective cooperative trials.

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