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Eur J Cancer, Vol. 27, No. 3 pp. 309–315, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Controversies in the Management of Non-Hodgkin Lymphoma

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INTRODUCTION

NON-HODGKIN lymphomas (NHL) represent a disseminated group of malignancies with heterogenous morphological, immunological and clinical characteristics. The rapidly increasing knowledge of the pathophysiology and histology of the immune response and the understanding of lymphocyte differentiation has led to the concept that NHL represent neoplastic counterparts of reactions which usually take place after antigenic stimulation. The course of NHL ranges from well tolerated, indolent malignancies to quickly proliferating, rapidly fatal tumours. Although much has been achieved, especially in the treatment of high-grade lymphoma, NHL are among the most challenging malignancies today. This paper intents to summarise some of the important issues and controversies in the management of NHL.

CLASSIFICATION

The classification of neoplastic lymphoid disorders has undergone substantial changes over the last decades. Since its introduction in 1956, the Rappaport classification [1] had been widely accepted as an easy reproducible and clinically relevant system. However, the validity of this classification became questionable when the functional and ontogenetic heterogeneity of the normal immune system was discovered. Consequently other classifications have been proposed, including those by Dorfmann [2], Bennet [3], Lukes and Collins [4], Lennert [5], and the WHO [6], but none have become widely accepted. The use of six different classifications for NHL throughout the world obviously made international analysis and comparison of clinical trials extremely difficult.

In an attempt to find a terminological compromise for the definition of entities that differed considerably regarding clinical course, prognosis and therapeutical implications, the so-called "working formulation" was introduced in 1982 [7]. The working formulation (Table 1) was not created as a new classification but as a means of translating one classification into another. It was based on the clinical follow-up information of 1175 previously untreated cases by pathologists representing the six different major classification systems. Utilising morphological and clinical criteria, 10 subtypes of NHL were subdivided into three prognostic groups: low-grade (median survival of 7 years), intermediate-grade (median survival: 3 years), and high-grade (median survival: 1 year). Being a simple, practical translation formula for interinstitutional and international comparisons, the working formulation does not employ immunologic methods in the study design.

A European rival, the Kiel classification [8], is based on morphological criteria and incorporates information derived from immunological and molecular biological techniques. The Kiel classification (Table 2) in its recently updated form [9] separates the NHL according to the B- and T-cell origin. Its discrimination between only two major groupings according to clinical behaviour (low-grade and high-grade) has proved relevant in determining treatment [10] although the identifi-

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Received 27 Nov. 1990; accepted 28 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.

Table 1. A classification scheme of the working formulation, modified for including some subcategories used in European clinical studies and expanded for peripheral T-cell malignant lymphomas

WF (main category)	B-cell subcategory	T-cell subcategory
A. Small lymphocytic	Lymphocytic (B)	Lymphocytic (T)
	Lympho-plasmocytoid	
	Prolymphocytic (B)	Prolymphocytic (T)
B. Follicular small-cleaved	Follicular	
	Diffuse areas	
C. Follicular mixed	Follicular	
	Diffuse areas	
D. Follicular large	Large cleaved	
	Large non-cleaved	
	Multilobated	
	Diffuse areas	
E. Diffuse small/medium	Intermediate lymphocytic	T-zone
	Mantle-zone	Small pleomorphus
	Small-cleaved	
F. Diffuse mixed	Follicular centre cells	Lymphoepithelioid
	Lympho-plasmacytic	Angioimmunoblastic-like
	polymorphous	
G. Diffuse large	Cleaved	
	Non-cleaved	
	Multi-lobated	
	Polymorphous	
H. Immunoblastic	Monomorphous (B)	Immunoblastic (T)
	Polymorphous (B)	Polymorphous (T)
		Clear/pale cells
I. Lymphoblastic	Lymphoblastic (B)	Lymphoblastic (T)
		Convoluted/non-convoluted
J. Small non-cleaved Burkitt's	Monomorphous	
	Polymorphous non-Burkitt	
Miscellaneous		
K.		Mycosis fungoides
L.	Extramedullary	
M.	plasmacytoma	
N. Composite	Large-cell anaplastic	Ki-1 +
O. Unclassifiable/Other		

Modified from Bryon and Berger [88].

cation of intermediate-grade lymphomas in the Kiel classification remains controversial. Due to the poor prognosis, centrocytic lymphoma is the most obvious candidate for a regrading as intermediate-grade lymphoma [11]. The predictive value of common classifications in NHL is currently being reversed by the changes of life expectancy due to improved chemotherapy resulting, paradoxically, in more long-term survivors with high-grade lymphoma than with some low-grade lymphoma.

IMMUNOHISTOLOGY AND MOLECULAR BIOLOGY

The use of monoclonal antibodies (MoAbs) has made it possible to clearly define the lineage and stage of differentiation of most malignant lymphoproliferative disorders, and has resulted in the concept that these malignancies can be related phenotypically and functionally to their normal counterparts in the immune system. The determination of B- or T-cell lineage in NHL is of clinical significance in a variety of lymphomas [12]. Monoclonal antibodies have identified new entities such as the CD30 antigen expressing Ki-1 lymphoma [13]. They discriminate between related entities: CLL or centrocytic lymphoma which express the CD5 antigen can be distinguished from CD5-negative lymphoplasmacytoid or plasmacytic lymphomas [14]. In addition, MoAbs may serve as tools to assess prognostic subgroups [15]. Studies with proliferation-associated anti-transferrin receptor (Tfr) monoclonal antibodies have indicated that high-grade NHL have higher Tfr-expression (mean 22.5%) then those of low-grade (mean 2.5) [16]. There appears to be a good correlation between the proliferation marker Ki-67 expression and histological classification into high-grade and low-grade lymphoma [17]. With the exception of these data, detailed immunophenotyping has little prognostic value when compared with conventional histopathology [18].

Clonality and lineage derivation of certain putative B- or T-cell malignancies can now be investigated by gene rearrangement studies using nuclear probes for human immunoglobulin (Ig) [19] and T-cell receptor (TcR) genes [20]. This approach can be used to distinguish monoclonal from polyclonal lymphoid proliferations, and to determine the lymphocytic lineage of neoplasms lacking lineage-specific surface determinants [21, 22] and see review by Brada (p. 315). Advantages of this technique include the requirement for only a small number of cells (about 10^6), and the ability to detect neoplastic cells in a proportion of 1% of the total population [23]. However, there is a need for clinical correlation and additional studies to decide whether a genotypic analysis of lymphoproliferative disorders is of prognostic significance or might perhaps influence therapy. Studies published recently by Hornig *et al.* [24] and Schauten *et al.* [25] failed to demonstrate any correlation between clonal gene rearrangement in the peripheral blood of patients with NHL and subsequent relapse. Other studies seem to identify prognostic subgroups, as in childhood B-cell acute lymphoblastic leukaemia (B-ALL) [26] or in AILD [27]. Despite great efforts in many laboratories and the fascinating implications for our understanding of the biology of NHL, DNA sequencing cannot be recommended at the present time for the routine management of NHL.

IDENTIFICATION AND MANAGEMENT OF NEW ENTITIES

MALT lymphomas

Lymphoid tissue is not restricted to lymph nodes but exists at other sites such as the spleen, mucosa and skin. Lymphocytes in the mucosa associated lymphoid tissue (MALT) probably develop in a very similar way to their nodal counterparts. A new concept of malignant lymphoma arising from MALT tissue has been proposed by Isaacson and Wright [28]. Examples of MALT lymphomas are Mediterranean lymphoma (alpha heavy chain disease) [29] and polymorphic B-cell lymphoma [30]. MALT lymphomas can be found in various localisations but are mainly related to the gastrointestinal tract. They are characterised by a tendency to remain localised until late in the course of the disease [31]. Since the biological concept of MALT lymphomas is still controversial at the moment [32], reconsiderations of clinical and morphological data are required. (See below for staging and treatment of primary gastric lymphoma.)

Table 2. Updated Kiel classifiation of non-Hodgkin lymphomas

B-cell	T-cell
Low grade	Low grade
*Lymphocytic-chronic lymphocytic and hairy cell leukaemia	Lymphocytic-chronic lymphocytic and prolymphocytic leukaemia
	Small, cerebriform cell-mycosis fungoides, Sezary's syndrome
Lymphoplasmacytic/cytoid	Lymphoepithelial (Lennert's)
Plasmacytic	Angioimmunoblastic (AILD, Lg X)
*Centroblastic/centrocytic	
follicular +/− diffuse	T-zone
diffuse	Pleomorphic, small cell
Centrocytic	(HTLV-1 +/−)
High grade	High grade
Centroblastic	Pleomorphic, medium and large cell (HTLV-1 +/−)
*Immunoblastic	Immunoblastic (HTLV-1 +/−)
*Large cell anaplastic (Ki-1)	Large cell anaplastic (Ki-1)
Burkitt's lymphoma	
*Lymphoblastic	Lymphoblastic
Rare types	Rare types

*Indicates some degree of correspondence, either in morphology, or in functional expression, between categories in two columns.
Adapted from [9].

Cutaneous T-cell lymphomas

Cutaneous T-cell lymphomas including mycosis fungoides and Sezary syndrome are indolent NHL associated with a proliferation of helper T-lymphocytes [33]. Clinical characteristic features are initial skin involvement with subsequent development of visceral disease. Since the appearance of early skin lesions varies widely, diagnosis has been extremely difficult and often requires consecutive biopsies. The demonstration of clonal T-cell receptor rearrangements might allow an earlier diagnosis [34]. The optimal treatment has yet to be defined. Modalities consist of a variety of measures including topical treatment (cortison, nitrogen mustard, nitrosoureas), electron beam radiotherapy, psoralen with ultraviolet light radiation (PUVA), systemic radiotherapy, systemic chemotherapy and biological response modifiers. A recent study with escalating doses of interferon (IFN-α) combined with PUVA has reported 12/15 complete remissions in pretreated patients [35]. Larger clinical studies comparing IFN-α with PUVA to IFN alone, to PUVA alone or to other standard therapies are needed.

AIDS-related NHL

Malignant lymphoma have become one of the major problems among the neoplastic complications of AIDS with an incidence of 4–10% of cases [36]. These lymphomas are mostly of high-grade B-cell type presenting in unusual extranodal sites like CNS and gastrointestinal tract, or, less frequently, rectum, orbit, gallbladder, adrenals, myocard or maxilla [37]. In contrast, low-grade lymphoma reported in HIV infected individuals do not appear to be of increased incidence and the behaviour of these tumours is not different from those occurring in the general population [38]. Ig heavy chain gene rearrangement studies identified two or more rearrangements suggesting multiclonality of B-cell lymphoma in AIDS patients [39].

The treatment of AIDS related NHL is still controversial. Though complete remissions are possible with multiagent chemotherapy [38, 40, 41], CNS relapses are frequent and the use of intrathecal prophylactic chemotherapy was not effective in all patients [42]. Low white blood cell counts during therapy are a particular problem. More aggressive regimens have failed to improve survival rates nor prevent the CNS relapse [42] but they do lend to considerable haematologic toxicity. Current attempts to prevent severe leukopenia involve the use of G-CSF or GM-CSF during chemotherapy with M-BACOD or CHOP (see footnotes to Tables 3 and 4 for abbreviations) and the application of zidovudine (AZT) in an effort to diminish opportunistic infections [36].

CONTROVERSIES IN THE TREATMENT OF NHL

Therapy of localised lymphoma

The diagnosis of localised NHL requires an extensive staging procedure including CT scans of the abdomen and the chest, bone marrow biopsy, lymphangiography, liver biopsy and, eventually, laparatomy. This is crucial, since involved field/extended field radiation can be highly effective in achieving long-term remissions but relapses occur in non-radiated sides [43]. In localised low-grade lymphomas (clinical stage [CS] I/IE, pathological stage [PS] I/IE), disease-free survival after radiation therapy is 60–90% at five years, being best in those patients who were pathologically staged [44–46]. In centroblastic and immunoblastic high-grade NHL, pathological staging before radiation therapy of localised stages is mandatory. Clinical staging only has been associated with up to 50% relapses within 2–5 years in patients with stages CS I and IE [47]. Based on these data, several centres have investigated the addition of polychemotherapy to radiotherapy in clinically staged patients of localised lymphoma. They reported CR rates (90–95%) and disease-free survival (70–100% after 2–5 years) that match those of patients in PS I/IE treated with radiation therapy alone. Chemotherapy is the therapy of choice for patients with generalised high-grade lymphoma (≥ CS II/II E) and all patients with lymphoblastic subtypes.

The management of primary gastric lymphoma (PGL) is still

Table 3. Treatment results of disseminated low-grade NHL (stage III/IV)

Therapy	No. of patients	% CR	Median RFS (months)	Actuarial survival (median)	Histology; stage	References
Daily SA	20	66	50	60+	NLPD, NML, DLWD; IV	73
Pulse CBL	33	33	40	60+	NLPD, NML, DLWD; III, IV	74
CVP	49	67	16	83	NLPD; III, IV	75
CVP	23	83	50	60+	NLPD, NML, DLWD; IV	73
C-MOPP	24	79	84	84+	NML; III, IV	76
COPP	27	56	84	90	NLPD; III, IV	77
TBI	17	71	14	48+	NLPD, NML, DLWD; III,IV	78
TBI	27	77	48	60	NLPD, NML, DLWD; III, IV	79
CVP-TLI-CVP	20	70	50	60	NLPD, NML, DLWD; IV	
ProMace-MOPP/TLI	51	71	45+	60+	NLPD, NML, DLWD, DLID; III, IV	51

SA = single alkylating agent, CBL = chlorambucil, C-MOPP/COPP = cyclosphosphamide, vincristine, procarbazine, prednisone, TBI = total body irradiation, CVP-TLI-CVP = CVP-total lymphoid irradiation-CVP, NLPD = nodular lymphocytic poorly differentiated lymphoma, NML = nodular mixed lymphoma, DLWD = diffuse lymphocytic well-differentiated lymphoma, DLIP = diffuse lymphocytic intermediate lymphoma.
Modified from Portlock [43].

controversial. As discussed above these lymphomas are thought to arise from mucosa associated lymphoid tissue (MALT). This kind of tumour has a tendency to remain localised and the overall prognosis is better than that of its nodal counterparts. Primary gastric lymphoma do not fit into any of the categories described in commonly used classifications. The most commonly used staging system is the one described by Musshoff [48]: he subdivides stage I into stage I_{E1} (without serosal effection) and stage I_{E2} (with serosal infiltration or perforation). Stage II_E can also be subdivided: stage II_{E1} (spread to intra-abdominal contiguous lymph nodes, i.e. para-aortic, iliac . . .). Since an increasing number of primary gastric lymphoma are being diagnosed by endoscopic biopsies, the role of primary surgery has become controversial. Recently published results [49] seem to indicate that some of the advantages claimed for surgery in primary gastric lymphoma, such as debulking and abatement of the risk of perforation or hemorrhage during chemotherapy or radiotherapy, have been overestimated in relation to the intrinsic surgical risk [50]. Furthermore, an operation delays the onset of potentially life saving radiation therapy or chemotherapy. Thus, surgery should be very carefully balanced against the expected anaesthesia surgical risk and can be avoided in disseminated stages (stage II_E and beyond). Though the number of cases with disseminated disease reported is very small and staging procedures as well as treatment modalities vary considerably, combined chemotherapy and radiotherapy seem to be more effective than chemotherapy or radiotherapy alone. The role of chemotherapy compared with radiation therapy with or without surgery requires further investigation and is currently being explored in prospective studies [50].

Disseminated low-grade lymphoma

Unlike high-grade NHL or low-grade NHL at localised stages, low-grade NHL of disseminated stages have a relapse-free survival of 60% at five years and continue to decrease through to the 10th year (40% relapse-free survival) of observation before a plateau may then become evident [43]. These findings have prompted clinicians to reconsider the "watch and wait" concept of the early 1980s [51] and have spurred new therapeutic approaches. Table 3 indicates the treatment results with chemotherapy and/or radiation therapy. Complete remission rates vary between 33–83%; median relapse-free survival is 14–84 months. These results are, however, difficult to interpret, since the studies include relatively few patients and compare different subtypes. In addition, relapse-free survival and overall survival are measured over many years, making "early" conclusions impossible. The impact of histology on the prognosis is highlighted by results published recently by the German lymphoma study group: in contrast to other low-grade NHL with a median survival of 4–5 years, median survival in centrocytic lymphoma was 2.5 years only [14]. A randomised comparison of COP vs. CHOP did not show a significant difference in survival [52].

Disseminated high-grade NHL

The advance of intensive combination chemotherapy has transformed high-grade NHL from an almost fatal disease to one that is curable in a certain proportion of patients. Table 4 summarises a comparison of the most commonly used chemotherapeutic regimens. Those of the first generation were characterised by cyclic repeated application of 4–5 drugs as in the CHOP regimen [53]. CR rates of 40–60% in previously untreated patients were reported, while only about one third achieved long-term remissions. Based on the Goldie–Coldmann tumour cell model [54] predicting that a reduced rate of tumour response is suggestive of emergence of resistant clones, non-cross resistant chemotherapy regimens like ProMACE/MOPP [55] and COP-BLAM/IMVP-16 [56] were introduced. The reported CR rates of up to 76% and relapse-free survival of approximately 50% indicate the superiority of these concepts. Newer developments like MACOP-B [57] and ProMACE-Cyta-BOM [58] appreciate the relevance of achieving CR as quickly as possible, thus reducing the duration of treatment to 3 or 4 months. The advanced generation COP-BLAM III, COP-BLAM IV and COP-BLAM V programs incorporate vincristine and bleomycin infusions rather than bolus injections [59, 60]. Although no randomised comparison has yet been performed, these modifications seem to improve CR by 10% and overall survival by 10–15% compared with the original COPBLAM regimen [61]. Since the initial observation that dose intensity may be important in the successful treatment of lymphoma [62], ultra high-dose

Table 4. Comparison of combination chemotherapeutic regimens for high-grade NHL

Generation	Regimen	CR rate (%)	Long-term survival (%)	Duration of therapy (months)	Reference
First	CHOP (>65yr)	—	12	6	80
	CHOP	47	<30	6	53
	COPA-Bleo	46	30	6	81
	COMLA	44	<33	9	82
	BACOP	48	35	6	83
	MOPP	41	35	6	84
	CAP-BOP	43	35	6	85
			35		
Second	COP-BLAM I	73	55	6	86
	M-BACOD	72	48	7	87
	COP-BLAM/IMVP-16 ProMace/MOPP	61 74	60 48	7 6	56 55
Third	COP-BLAM III	84	65	8	59
	MACOP-B	84	63	3	57
	ProMace-Cyta-BOM	79	60	4–6	58

CR = complete response, MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin, ProMACE = - prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, CytaBOM = cytarabine, bleomycin, vincristine, methotrexate, MOPP = mechlorethamine, vincristine, procarbazine, prednisone, M-BACOD = methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, COP-BLAM = cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine, BACOP = - bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, COPA-Bleo = cyclosphosphamide, vincristine, prednisone, doxorubicin, procarbazine, bleomycin, CAP-BOP = cyclophophamide, doxorubicin, procarbazine, bleomycin, vincristine, prednisone, COMLA = - cyclophosphamide, vincristine, methotrexate, leucovorin, cytarabine.

chemotherapy with autologous bone marrow transplantation (ABMT) has been introduced. With ABMT, cures can be achieved in patients who are unlikely to be cured by conventional chemotherapy [63] and see review by Philip and Biron (p. 320) The discrepancy between the intended dosage and the actual delivered doses may explain, in part, the discrepancy between results among groups testing the same drug combinations. Other factors hampering the comparison of definite cure rates are the heterogenous patient selection (age, stage, histology) and the short follow-up periods.

IMMUNOTHERAPY

Biological response modifiers have been found to have activity in low-grade NHL. Recombinant IFN-α yields mostly partial responses with a median duration of 6–12 months in up to 50% of patients [64]. The maximal effective dose and treatment schedule, however, is still a matter of controversy. Prospective trials are evaluating a potentially additive or synergistic activity of rIFN-α combined with chemotherapy. Monoclonal antibodies against B-cell antigens or anti-idiotypic antibodies have been used as single agents [65, 66], in combination with rIFN-α [67] or as radiolabelled immunoconjugates [68]. Press *et al.* describe 4/5 CRs with ^{131}T labelled anti-CD37 monoclonal antibodies in patients with low or intermediate grade lymphomas who had failed conventional treatment [69]. These patients were selected by biodistribution studies indicating low tumour burden and sufficient homing to tumour cells. Other fascinating approaches include the use of immunotoxins, i.e. monoclonal antibodies linked to toxins such as ricin-A [70] or saporin [71]. Ongoing phase I/II clinical trials with anti-CD22 ricin-A-chain immunotoxins indicate up to 50% response rates in patients with resistant or relapsed B-cell lymphoma [72]. However, at the moment it is too early to judge the general applicability of these approaches.

CONCLUSIONS

Over the past decades, improved diagnostic and therapeutic modalities have led to a better understanding of non-Hodgkin lymphoma resulting in better chances of cure for many patients. Still, many questions and controversial issues remain. One key problem is the ongoing confusion in the classification of NHL. The Kiel classification in its updated version has proven clinical significance, particularly when taking immunological and biological aspects into account, and it might therefore find more and more acceptance. Immunobiology and molecular biology will further extend the knowledge of the biology of NHL and help to define new clinical entities. As a result, clinical studies using various modalities, including immunotherapy, in precisely defined entities may improve treatment strategies and help avoiding treatment related morbidity and mortality.

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Acknowledgement—We thank Dr Bernd Lathan for his valuable comments on the manuscript and Hedwig Roden for her excellent secretarial assistance.

Eur J Cancer, Vol. 27, No. 3, pp. 315–320, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Impact of Molecular Biology on Our Understanding of Non-Hodgkin Lymphoma

M. Brada

INTRODUCTION

NON-HODGKIN lymphoma (NHL) is a clonal expansion of B or T lymphocytes during various stages of differentiation. A number of non-random chromosomal rearrangements and translocations have long been recognised, the most frequent of which are t(8;14) and t(14;18). Molecular analyses of chromosomal rearrangements have identified genes adjacent to the breakpoint sites which are deregulated and are considered to play an important role in oncogenesis. The majority of translocations identified also involve immunoglobulin genes in B-cell and T-cell receptor genes in T-cell neoplasms. Intensive research effort is directed at molecular studies of these and other less frequent chromosomal alterations with the aim of defining mechanisms and detecting new genes involved in oncogenesis. For the clinician the increased understanding of the individual steps of oncogenesis and their regulation provides a potential target for therapeutic intervention. The maturation of lymphoid cells is accompanied by rearrangement of immunoglobulin (Ig) and T-cell receptor (TCR) genes as part of the normal mechanism of generating Ig and TCR diversity. Specific rearrangements and translocations can be exploited as clonal markers in diagnosis and monitoring of disease.

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Received 21 Nov. 1990; accepted 28 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.

MOLECULAR EVENTS

Immunoglobulin and TCR genes

The somatic rearrangement of Ig and TCR is a mechanism for generating antibody and TCR diversity [1]. Rearrangement of Ig gene occurs early in lymphoid maturation and follows a defined sequence of recombination steps of initial joining of Diversity (D) and Joining (JH) genes followed by VHDJH joining (VH = variable region gene). Heavy chain rearrangement is followed by κ and λ light chain recombination (for review see Alt *et al.* [2, 3]). The rearrangement of heavy chain and light chain genes is specific for each B-cell and its clone. However,