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Distinct Entities Among Low-grade Non-Hodgkin's Malignant Lymphomas. Analysis of a Series of 377 Cases

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Abstract—*A series of 377 low-grade non-Hodgkin's lymphomas, observed in the same Institute, was analysed. Pathological types following the Kiel classification were crossed with the usual parameters of patients (sex, age) and disease (tumoural extension, main anatomical involvement, biological data, course of the disease). Small differences appeared for the survivals for the overall series. By contrast many significant differences were observed for sex, age, dissemination of the disease, special tissue involvement, monoclonal gammopathy, complete remission rate and further involvement in case of relapse. These parameters allow one to distinguish different clinico-pathological entities after the morphological cellular features. Such correspondences appear meaningful and might be offered by any other classification which should not be based only on the prognosis.*

INTRODUCTION

CLASSIFICATION of malignant lymphomas other than Hodgkin's disease or non-Hodgkin's lymphomas (NHL) was discussed for a long period before Rappaport proposed in the sixties a nomenclature based on the assumption that lymphomas were either lymphoid or reticular and had always first a nodular then a diffuse pattern [1]. The modern classifications, however, appeared in the early seventies. They were based on new immunological data. Simultaneously two classifications were proposed by Lukes and Collins [2] and by Lennert [3]. This latter classification was well appreciated and experienced wide use particularly in Europe [4, 5]. From a clinical point of view, its main advantage was to distinguish accurately two main groups of NHL, so called low-grade malignancy, with a rather slow course and good prognosis, and high-grade malignancy, with spontaneously rapid course and poor prognosis. The possibility of evaluating the prognosis from the pathological specimen with a routine procedure appeared as a worthy advance, mainly for the clinicians in charge of treating patients. Thus further attempts were made to improve and, if possible, to simplify the distinction between 'good' and 'poor' NHL. The last of them gave the Working Formulation for International Usage [6] which can be considered as a compromise between the different previous propositions.

However, these trends lost from view the fact that the Kiel classification also had the advantage of affording other correlations with clinical parameters different from the course of the disease. Many of these clinico-pathologic correlations were suggested by Lennert [4]. We previously demonstrated many significant differences among the high-grade NHL, mainly between lymphoblastic and immunoblastic types [7]. We reproduced the same kind of study for low-grade NHL and show in this paper that the same is true, i.e. there are, among this group of NHL, different entities characterized by a variety of clinical, biological and evolutive data.

PATIENTS AND METHODS

Seven hundred and forty patients with NHL were seen before any treatment, treated and followed in our Institute from January 1965 to December 1982. The diagnosis of NHL was reviewed and confirmed in all cases in our Institute. It was classified according to the Kiel classification retrospectively for patients before 1976 and then after in each case before any treatment. Three hundred and seventy-

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seven (51%) of these cases were classified as low-grade (LG) malignancy as one of the four main following types: lymphocytic (LC), lymphoplasmacytic (LP), centroblastic-centrocytic (CB-CC) and centrocytic (CC). Patients diagnosed with LC-NHL on lymph node biopsy who also had pathological lymphocytes in the blood on routine examination were considered as having a chronic lymphocytic leukaemia (CLL) and excluded from this study. CB-CC NHL were subclassified as nodular or nodular and diffuse, following the predominant architectural pattern. For some analyses CB-CC and CC were put together as follicular lymphomas (FL) after their origin in the follicles of the lymphoid tissues.

All patients were investigated in the same way, whatever the exact type of their NHL, with a full clinical examination, chest X-ray, lymphography (except for a few patients too old or investigated by CT-scan in the last few years), bone marrow analysis by puncture and/or biopsy and routine blood investigations. No liver biopsies or exploratory laparotomies were performed. Obviously the treatment evolved over this period. For patients seen before 1976 it was independent of the pathological type which was not known in due time. Most patients received a combination of radiotherapy and chemotherapy, except in the case of disseminated and non-bulky disease in which chemotherapy only was given, according to a previously described treatment programme [8]. For more recently treated patients, treatment became different for high-grade and for LG-NHL. Among this latter group total body irradiation was introduced and treatment was heavier for some patients considered as having intermediate malignancy, i.e. CB-CC nodular and diffuse and CC, after our first analysis using the Kiel classification [9].

All patients were followed up until their death or 1 October 1986. Median follow up was 88 months. Only two patients were lost of follow up after 62 and 164 months.

For all the 377 patients the following parameters were analysed: (1) age and sex, (2) histological type, (3) extension of the disease: clinical stage, number and sites of involved areas, general symptoms, diameter of the main tumour, (4) biological parameters: blood cell values, erythrocyte sedimentation rate (ESR), monoclonal gammopathy, (5) treatments, (6) results: complete remission, disease-free survival, crude survival, (7) course: type and localization of first or further relapse.

The chi square test or Fisher's exact probability test for small group were used for statistical analysis. The survivals were calculated according to the Kaplan–Meier method and compared following the log-rank test.

Table 1. Distribution of sex (figures are percentages)

	Males	Females	
LC	64.7	35.3	
LP	67.9	32.1	$P = 0.04$
CB-CC	49.4	50.6	
CC	53.3	46.7	

RESULTS

The distribution of the 377 cases of this series of LG-NHL is as follows: 51 LC, 53 LP, 243 CB-CC (145 nodular, 98 nodular and diffuse), 30 CC.

The distribution of the sex of patients is shown in Table 1. There is a male predominance for LC and LP and an equivalence of males and females for CB-CC and CC ($P = 0.04$). Age is shown in Table 2. Patients with CB-CC are significantly younger than patients with other NHL. Furthermore, among patients with CB-CC, those with CB-CC nodular are significantly younger than those with CB-CC nodular and diffuse ($P = 0.006$).

Extension of disease, as shown by staging, is detailed in Table 3. The total number of involved areas is significantly higher in patients with LC. Lymphography is less frequently abnormal in LP and CC. Stages are higher in LC and lower in LP than in FL (CB-CC + CC). Involvement of particular sites appears also significantly different among different types of LG-NHL (Table 4). For primary involvement, before any treatment, bone marrow involvement is more frequent in LC, GI tract and facial involvement in LP. Secondarily, during the course of the disease, skin involvement is observed in LC and LP, while blood passage of lymphoma cells occurs the most frequently in LC ($P \leq 0.04$) and to a lesser extent in CC.

Among biological properties, ESR appears significantly higher in LP ($P < 0.02$), in correlation with the presence of a monoclonal gammopathy (16.6% vs. 13.5% in LC, 1.2% in CB-CC and 0% in CC; $P < 0.001$) and with a lower level of erythrocytes in LP ($P = 0.037$).

No significant difference was observed as far as treatment is considered. However the rate of complete remission after primary treatment was significantly lower in LC (52.0% vs. 75.5% in LP, 79.8% in CB-CC, 63.3% in CC; $P = 0.0005$).

Finally disease-free survival and crude survival are shown in Figs 1 and 2. LC patients appear to have the worst disease-free survival, whereas CB-CC patients have the best disease-free survival and survival. There is no difference between patients with nodular or nodular and diffuse CB-CC.

Table 2. Age of patients

	Mean	S.D.	
LC	64.7	11.7	
LP	63.5	12.6	$P = 0.001$
CB-CC	58.1	14.4	$P = 0.009$
CC	63.7	11.1	$P = 0.033$
CB-CC			
Nodular	55.9	13.7	
Nodular and diffuse	60.9	14.8	$P = 0.006$

Table 3. Tumoural extension (figures are percentages)

	Number of involved areas* (mean; S.D.)	Abnormal lymphography†	Stages‡ I + II	Stages‡ III + IV
LC	5.8; 3.8	51.0	33.3	66.7
LP	4.1; 3.5	37.7	54.7	45.3
CB-CC	4.5; 3.5	57.0	41.8	58.2
CC	4.6; 3.5	43.3	41.3	58.7

*LC vs. LP: $P = 0.015$; LC vs. CB-CC: $P = 0.022$.
†LP vs. CB-CC: $P = 0.008$.
‡LC vs. LP: $P = 0.01$; LP vs. CB-CC: $P = 0.065$.

Table 4. Particular localizations (figures are percentages)

	Primary			Secondary	
	Bone marrow*	GI tract†	Facial‡	Skin§	Leukaemia‖
LC	40.8	4.0	6.0	6.0	26.0
LP	17.3	13.2	17.0	7.5	5.7
CB-CC	16.4	3.7	0.4	1.6	4.5
CC	23.3	6.7	0	0	13.3

*LC vs. LP: $P = 0.003$; LC vs. CB-CC: $P < 0.001$; LC vs. CC: $P = 0.057$.
†LC vs. LP: $P = 0.037$; LP vs. CB-CC: $P = 0.005$.
‡LC vs. LP: $P = 0.001$; LP vs. CB-CC: $P < 0.001$; LP vs. CC: $P < 0.001$.
§LP vs. CB-CC: $P = 0.021$; LP vs. CC: $P = 0.052$.
‖LC vs. LP: $P < 0.001$; LC vs. CB-CC: $P < 0.001$; LC vs. CC: $P = 0.040$.

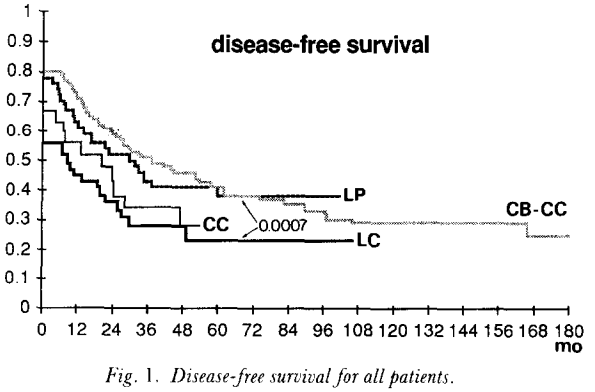

Fig. 1. Disease-free survival for all patients.

DISCUSSION

This analysis was made on a large series of LG-NHL. The long period during which patients were observed incites to be careful before accepting all the results in detail. However, treatments were homogeneous during all this period. Moreover modifications of treatments resulted only in light and non-significant improvement of overall survival of patients as previously observed [8]. These variations were the same whichever the exact pathological type, except for reinforcement of treatment in the second decade for CB-CC nodular and diffuse

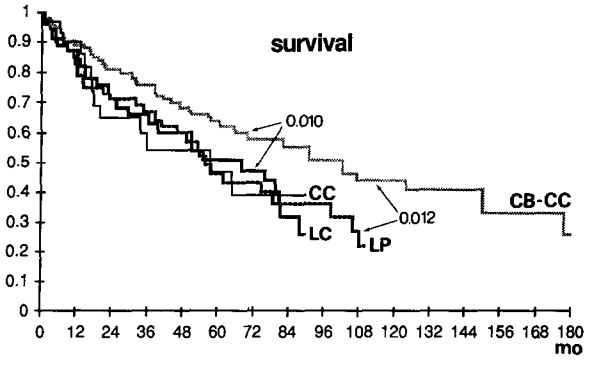

Fig. 2. Crude survival for all patients.

and CC as detailed in the material and methods section. In summary influence of treatment appears to be limited in these LG-NHL. Thus comparison between different types of LG-NHL appeared possible without major bias. Following the number of comparisons we performed, significant differences with $P < 0.05$ due only to chance were expected to be no more than three whereas the observed significant differences were far more numerous and often with a very low P value. Other observed differences, some of them probably meaningful, did not reach significance and are thus not given here.

In the Kiel classification all these lymphomas are put together in the large group of LG-NHL. However their slow course does not appear to be the only characteristic parameter. Furthermore, it may be discussed since many of these NHL may present a tumoural progression, as already outlined by Lennert [5].

By contrast there are many other parameters which allow one to distinguish, after the morphological aspects of malignant cells, different main types of LG-NHL. In short LC appear as the most disseminated LG-NHL as shown by the number of involved areas, by the clinical stages, by the frequency of pathological lymphography and by the initial involvement of bone marrow. Furthermore during the course of the disease blood passage of malignant cells is frequent, arguing the closeness of this type of LG-NHL and of CLL. LC-NHL show also a poor rate of complete responses which explains that the disease-free survival is the worst of all LG-NHL. The overall survival is rather poor, perhaps due to the presence among all the LC of some T-zone LC which have a poorer prognosis [5]. We did not analyse this last point.

LP-NHL are less disseminated, as documented by the number of involved areas, the lymphography and the stage. They involved particularly anatomical sites other than lymph nodes as quoted previously by Lennert [5], namely GI tract, facial structures (especially orbit and ocular apparatus) and secondarily skin. Chemosensitivity is good and chemotherapy when added to radical radiotherapy significantly improved the prognosis of stages I and II as observed previously [10]. A frequently associated monoclonal gammopathy explains probably the higher ESR (the equivalent presence of monoclonal gammopathy in LC may be due to pathological confusion as quoted by Lennert [5]).

CB-CC-NHL are the most frequent type of LG-NHL (51%). This high proportion may explain the earlier misinterpretation of Rappaport who considered that all NHL were first nodular at the beginning of the disease [1]. The significant difference of age (5 years; $P = 0.006$) between patients with CB-CC nodular or nodular and diffuse substantiates the idea that follicular NHL keep first a nodular pattern before becoming with time less nodular and more diffuse. In contrast with other NHL which show a male predominance, CB-CC-NHL have an equal distribution between the sexes.

This latter feature is also observed in CC-NHL which are observed in older patients. They present more frequently secondary blood passage of malignant cells. Complete remission is more rare and prognosis worse in comparison with CB-CC.

All these differences appear important because they substantiate the distinction of true different entities among LG-NHL. Many of them were already observed by Brittinger *et al.* [11] whose analysis is difficult to compare with ours. These entities are certainly not completely different one from the other which is easily understandable because of the vicinity of cells involved in the tumoural process and of the possibility of change among these cells during tumoural progression. Moreover there are some subdivisions inside each entity and improvements in immunological and morphological recognition allow the characterization of new and rare subtypes. Finally new methods of diagnosis appear thanks for example to particular chromosome or DNA rearrangements [12–14].

Awaiting the development of these new methods on a routine basis, our results suggest that at the present time it would be advisable to cease classifying NHL only by prognosis. By contrast one must take into account many clinical parameters besides the morphological cellular characteristics. Any classification must offer a coherent view of all the main clinico-pathological features of each NHL.

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