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A Clinicopathologic Study in Advanced non-Hodgkin's Lymphomas Treated with Sequential non-Cross-resistant Regimens: Comparison of the Working Formulation with the Rappaport and Kiel Classifications

S. MONFARDINI,* F. RILKE,† P. VALAGUSSA,* E. BAJETTA,* R. CANETTA,* R. BUZZONI,* R. GIARDINI† and S. VIVIANI*

*Divisions of *Clinical Oncology F and †Pathology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy*

Abstract—*One-hundred and ninety-four adult patients with histologically proven stage III and IV non-Hodgkin's lymphomas, treated with CVP (cyclophosphamide, vincristine and prednisone) alternated with ABP (adriamycin, bleomycin and prednisone), were analyzed to test the validity of the clinicoprognostic correlation offered by the working formulation in comparison with the Rappaport and Kiel classifications. Actuarial overall survival at* 5 yr *showed a significant difference among the three prognostic subgroups of the working formulation (low grade,* 53.3%; *intermediate grade,* 47.5%; *high grade,* 27.7%). *Overall survival of favorable subgroups of the Rappaport and Kiel classifications was superior to that of unfavorable prognostic groups. The percentage of systemic symptoms and bulky disease increased in patients with low-grade compared to those with intermediate-grade and intermediate-to-high-grade malignancy. The achievement of complete remission was not related to any of the prognostic groups of the Working Formulation, and no difference could be detected within the various prognostic groups of the Rappaport and Kiel classifications. Within the diffuse histiocytic lymphomas of the Rappaport classification, two groups with a different prognostic outcome were evidenced by the working formulation (G, with an overall survival of* 50%, *and H, with an overall survival of* 26.7% *at* 5 yr) *and by the Kiel classification. The possibility of reporting results in the three different groups of the working formulation instead of two can be considered a step forward. Within the diffuse histiocytic histology, the working formulation allows separation, as does the Kiel classification, into two main different prognostic subgroups.*

INTRODUCTION

THE PATHOLOGICAL classification of non-Hodgkin's lymphomas (NHL) has long been a controversial subject. This is due, at least in part, to the different approaches and terminology used by histopathologists. Medical oncologists and hematologists, often relatively uninformed on one or more of the six major available classifications (Rappaport, BNLI, Dorfman, Kiel, Lukes and Collins, WHO) [1–12], cannot adequately assess recent published data concerning NHL. However, it has recently been shown, by a study sponsored by the National Cancer Institute on a large case series, that all six classifications are valuable and comparable in reproducibility and clinical correlations [13]. As a result of this analysis, a 'working formulation' for clinical usage has been developed. Previous proposals of classifications have failed to achieve a general agreement [14–16] but still deserve the merit of having made an effort to develop a common classification.

The case material analyzed in the study that led to the working formulation was drawn from four institutions and therefore cannot be considered homogeneous with respect to the treatment

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applied. Also, early (stages I and II) and advanced (stages III and IV) cases were considered together in the study. We therefore think that additional analyses on case series at the same stage and receiving the same treatment are needed to further validate this working formulation.

To eliminate from the study as many prognostic variables as possible other than histology, a group of patients homogeneous for age, extent of disease (stages III and IV) and type of treatment (combination chemotherapy) was analyzed. The goal of the analysis was (1) to test the validity of the clinico-prognostic correlation offered by the working formulation compared to the Rappaport and Kiel classifications in patients with advanced NHL uniformly treated with combination chemotherapy; and (2) to determine the value of the working formulation in terms of the clinical significance of the morphological subdivision of diffuse histiocytic lymphoma (DH). For a comparison of the new formulation we chose the Rappaport classification, since it is almost a historical milestone and represents the first successful attempt to provide a more valuable tool than those previously employed, and the Kiel classification, which is the most widely used in Europe.

MATERIALS AND METHODS

Adult patients (194) with histologically proven stage III or IV NHL treated at the Istituto Nazionale Tumori of Milan from November 1974 to March 1981 were considered in the present analysis. All cases were consecutive except for patients under 16 or over 71 yr of age and those with extensive prior chemotherapy. Patients still on therapy at the time of the present analysis with the leukemic phase of lymphoma, previous or concomitant malignancy, mycosis fungoides or malignant histiocytosis were not included in the present evaluation.

Histological diagnosis on biopsy material was obtained in all patients, and slides were reclassified for each case by one pathologist (F.R.) following the histological criteria of the Rappaport and Kiel classifications and those given for the working formulation. Translation of the categories of the Rappaport classification into the subentities of the working formulation is easily achieved. However, DH lymphomas have to be separated into diffuse, large cell, cleaved and noncleaved, and immunoblastic cell types. Different problems are intrinsic to the translation of the Kiel classification into the working formulation [17]. The accomodation of the lymphoplasmacytic immunocytoma in group A of the working formulation is acceptable with the exception of the polymorphic variant, which has to be moved to subgroup F. Follicular (centroblastic–centrocytic) lymphomas are not subdivided in the Kiel classification, although a useful method to count the small cell component can easily be applied [18]. The diffuse centroblastic–centrocytic lymphomas are classified as F, and the small number of large cell centrocytic together with the centroblastic as G.

The subgroups of the working formulation and the Kiel and Rappaport classifications are shown in Table 1. Lymphomas with coexistent follicular and diffuse paterns are included in the nodular group, although there is a tendency to do the opposite [19].

Clinical and pathological staging procedures were carried out as recommended at the Ann Arbor Conference [20]. Bilateral (Jamshidi) marrow biopsy from posterior iliac crests was obtained in all patients. Laparoscopy with multiple liver biopsies was done in all patients, except for those who showed marked clinical and biochemical evidence of liver involvement associated with rapidly progressive disease. Despite negative bone marrow biopsies, they were all classified as stage IV on clinical grounds. Additional diagnostic procedures (gastroduodenoscopy, rectosigmoidoscopy, roentgenograms of the GI tract, intravenous urography, brain and bone scan, etc.) were carried out only if required by specific clinical situations. Tumor lesions larger than 10 cm were defined as bulky disease.

Chemotherapy consisted of alternating cycles of CVP (cyclophosphamide, vincristine, prednisone) and ABP (adriamycin, bleomycin, prednisone) regimens, as reported elsewhere [21]. The status of complete remission (CR) was evaluated after a minimum of six cycles in patients who showed disappearance of all signs and symptoms of disease. In these patients pathological restaging was performed by repeat biopsies of initially involved extranodal sites. If the invasive procedures confirmed the achievement of CR, six additional consolidation cycles with the same alternating chemotherapy were given, and treatment was then discontinued. Patients who relapsed after CR following a new restaging were retreated with the initial alternating regimen (not to exceed the total cumulative dose of 550 mg/m^2 for adriamycin and 220 mg/m^2 for bleomycin). In those patients who approached a high cumulative dose of adriamycin and/or bleomycin, CVP alone was administered in the presence of continuous response. The entire treatment program was carried out on an outpatient basis. In the presence of progressive disease, miscellaneous treatments as required by clinical situations were adopted. Twenty-five patients had received prior inadequate radio-

Table 1. *The working formulation of non-Hodgkin's lymphomas for clinical usage (equivalent or related terms in the Rappaport and Kiel classifications are shown)*

Rappaport	Working formulation	Kiel
	Low grade	
Lymphocytic well-differentiated (LWD)	A. *Small lymphocytic* consistent with CLL plasmacytoid	lymphocytic (CLL) lymphoplasmacytic: lymphoplasmacytoid (LPL)
Nodular lymphocytic poorly differentiated (NLPD)	B. *Follicular* *predominantly small cleaved cell* diffuse areas sclerosis	Centroblastic-centrocytic (CB-CC) (small), follicular ± diffuse
Nodular mixed (NM)	C. *Follicular* *mixed, small cleaved and large cell* diffuse areas sclerosis	
	Intermediate grade	
Nodular histiocytic (NH)	D. *Follicular* *predominantly large cell* diffuse areas sclerosis	centroblastic-centrocytic (CB-CC) (large), follicular ± diffuse
Diffuse lymphocytic, poorly differentiated (DLPD)	E. *Diffuse* *small cleaved cell* sclerosis	centrocytic (CC) (small)
Diffuse mixed (DM)	F. *Diffuse* *mixed, small and large cell* sclerosis epithelioid cell component	lymphoplasmacytic/-cytoid, polymorphic (LPL, polym.) centroblastic-centrocytic (CB-CC) (small), diffuse
Diffuse histiocytic (DH)	G. *Diffuse* *large cell* cleaved cell Non-cleaved cell sclerosis	centroblastic-centrocytic (CB-CC) (large), diffuse centrocytic (large) (CC-LG) centroblastic (CB)
	High grade	
Diffuse histiocytic (DH)	H. *Large cell, immunoblastic* plasmacytoid clear cell polymorphous epithelioid cell component	Immunoblastic (IB) T-zone lymphoepithelioid cell
Lymphoblastic (LB)	I. *Lymphoblastic* convoluted cell non-convoluted cell	lymphoblastic (LB), convoluted cell type lymphoblastic (LB), unclassified
Undifferentiated (DU)	J. *Small non-cleaved cell* Burkitt's follicular areas	lymphoblastic (LB), Burkitt's type and other B-lymphoblastic
	Miscellaneous	
	composite mycosis fungoides histiocytic extramedullary plasmacytoma unclassifiable other	— mycosis fungoides — ML plasmacytic — —

therapy or chemotherapy. The median follow-up from the end of chemotherapy was more than 2 yr (range 2–83 months).

Comparisons between subgroups were done using the chi-square test. Relapse-free and survival distributions were calculated using the actuarial life-table method, starting from the day of initial treatment up to the closing date for the present analysis. The statistical significance of differences observed among various subgroups of patients was assessed by the log-rank test [22]. Percentages of patients free of disease, free from relapse or surviving are reported in the text and in the tables for one point in time (5 yr), as derived from life plots.

RESULTS

The analysis of our case series according to the three classification schemes is shown in Table 2. According to the working formulation, almost half of the cases were classified as intermediate-, about 30% as low- and a small group as high-grade. However, the high-grade group according to the Kiel classification and especially the unfavorable group of the Rappaport classification comprised a much higher percentage of cases (>41% and >68% respectively). According to the working formulation, the subgroups coded as D and J included only two cases, whereas there was an almost equal distribution among subgroups E, F and G within the intermediate group. Within the high-grade group, subtype H included the same percentage of cases as did subtypes E, F and G. The working formulation allowed a clear separation betwen the two equivalent groups G and H (diffuse large cell and large cell immunoblastic lymphoma). This distinction was found in an almost equal percentage of cases between centroblastic and immunoblastic according to the Kiel classification, whereas in the Rappaport classification there was a confluence only within the DH group (almost one-third of all cases).

Table 3 shows the distribution of the main conventional clinical features according to the various subgroups of the working formulation. The sex ratio was in slight favor of males in almost all subgroups of the working formulation. The ratio was 1:1 within the high-grade subgroup. The percentage of systemic symptoms increased from patients with low- to intermediate- and intermediate- to high-grade malignancies (low-grade, 20.7%; intermediate-grade, 24.7%; high-grade, 43.7%). The same was true for bulky disease, where the incidence was 8.6% in the low-, 21.5% in the intermediate- and 25% in the high-grade group. The highest incidence of systemic symptoms was found in F (28.6%), G (33.3%) and H (43.3%) subtypes. The incidence of bulky disease was 25% for F, 23.3% for G and 26.7% for H subtypes. No clear correlation could be established among the main prognostic subgroups and stage (III, IV). The analysis of the same clinical characteristics according to the Rappaport classification showed an incidence of B symptoms in 18.8% and bulky disease in 10.4% of patients with nodular histology and in respectively 28.4 and 20.2% of those with diffuse histology. Within the unfavorable histology, DH was associated with a high incidence of constitutional symptoms (37.1%) and bulky disease (24.2%). Systemic symptoms were present in 34.5% and bulky disease in 24.7% of cases with high-grade histology (Kiel), compared to 18.9 and

Table 2. Histological subgroups in 194 lymphoma patients

Working formulation	No.	%	Rappaport	No.	%	Kiel	No.	%
Low grade	58	9.9	nodular	48	24.7	low grade	106	54.6
Intermediate grade	93	47.9	diffuse	132	68.0	high grade	81	41.7
High grade	32	16.5						
A	12	6.2	DLWD	10	5.2	CLL	2	1.0
B+C	46	23.7	NLPD	39	20.1	LPL	8	4.1
			NM	9	4.6			
D	2	1.0				CC	31	16.0
E	33	17.0	DLPD	33	17.0	CB–CC	61	31.5
F	28	14.4	DM	27	13.9	T-zone	7	3.6
G	30	15.5	DH	62	32.0	LPL, polymorphic	11	5.7
H	30	15.5				CC–LG	4	2.1
			LB	2	1.0			
J	2	1.0						
			Lennert	3	1.5	CB	26	13.4
Unclassified	11	5.7	unclassified	9	4.7	IB	28	14.4
						Lennert	3	1.5
						unclassified*	11	5.7

*Low grade 4, high grade 3.

Table 3. Main clinical features according to the various subgroups of the working formulation in 194 patients

	Sex (M/F)	Stage (III/IV)	Systemic symptoms (A/B)	Bulky disease (no/yes)
Low grade	31/27	21/37	46/12	53/5
Intermediate grade	54/39	35/68	70/23	73/20
High grade	16/16	11/21	18/14	24/8
A	8/4	3/9	9/3	12/0
B+C	23/23	18/28	37/9	41/5
D	1/1	2/0	2/0	2/0
E	19/14	4/29	28/5	27/6
F	18/10	8/20	20/8	21/7
G	16/14	11/19	20/10	23/7
H	16/14	11/19	17/13	22/8
J	0/2	0/2	1/1	2/0
Unclassified	5/6	1/10	9/2	8/3
Total	106/88	58/136	143/51	158/36

14.5% respectively of patients with low-grade malignancies. Constitutional symptoms were present in 34.6% of patients of the centroblastic subgroup and in 46.4% of those of the immunoblastic subgroup. Bulky disease was evidenced in 23.1% of cases of the centroblastic subgroup and in 28.6% of the immunoblastic subgroup.

Further analysis taking into consideration the initial sites of involvement showed that there was an increased incidence of liver (36.9%), spleen (43%) and bone marrow (27.6%) localizations in the low-grade group of the working formulation compared to intermediate- (respectively 25.9, 29.1 and 21.5%) and high-grade malignancies (respectively 15.6, 15.6 and 9.4%). No relevant differences could be evidenced for Waldeyer's ring, skin, mediastinum, bone or lung. The same was true for the nodular (Rappaport) and low-grade (Kiel) groups.

The achievement of CR could not be related to any of the subgroups of the working formulation (Table 4). No difference could be detected within the various subgroups of the other two classifications. The achievement of CR could not be directly correlated with the main prognostic groups of the working formulation, or Rappaport or Kiel classifications.

The analysis of relapse-free survival (RFS) did not show a statistically significant advantage of low- and intermediate-grade vs high-grade malignancies of the working formulation (Table 5). The difference in RFS between low- and high-grade groups of the Kiel classification was also not statistically significant, and no relevant difference in RFS could be found between nodular and diffuse histology. A consistent tendency to progression was evidenced for cases with low- and intermediate-grade malignancies, whereas for high-grade malignancies no progressions were

Table 4. Percentage complete response related to histological subgroups

Working formulation	%	Rappaport	%	Kiel	%
A	75.0	DLWD	70.0	CLL	0
B+C	60.9	NLPD	61.5	LPL	87.5
		NM	66.7	CC	48.4
D	100.0				
E	48.5	DLPD	48.5	CB-CC	65.6
F	57.1	DM	66.7	T-zone	71.4
G	63.3	DH	62.9	LPL, polymorphic	54.5
H	60.0	DH	62.9	CC-LG	50.0
		LB	50.0	CB	65.4
J					
		Lennert	0	IB	57.1
Unclassified	81.8	unclassified	77.8	LB	50.0
				Lennert	0
				unclassified	81.8

Table 5. Complete response (%) and 5-yr relapse-free survival (RFS) in the main prognostic subgroups of the working formulation (W.F.) and Rappaport (R) and Kiel (K) classifications

Classification and prognostic subgroups		CR	RFS	Comparison	P
W.F.	Low grade	63.8	39.5	vs intermediate	0.96
	Intermediate grade	57.0	40.5	vs high	0.12
	High grade	59.4	44.8	vs low	0.08
R	Nodular	62.5	34.2	vs diffuse	0.72
	Diffuse	60-6	46.0		
K	Low grade	62.3	43.9	vs high	0.16
	High grade	60.5	41.8		

observed after 2 yr. Neither were any progressions observed in the high-grade subgroup of the Kiel classification until after 3 yr. However, the most valuable information was obtained from overall survival at 5 yr, which was, according to the working formulation, significantly different among the three groups (Fig. 1). As regards the Rappaport classification, survival at 5 yr was 55.8% for nodular vs 41.7% for diffuse histology ($P = 0.003$), whereas it was 49.9% for the low-grade vs 38.6% for high-grade malignancy of the Kiel classification ($P < 0.001$).

Analysis of the clinical significance of the morphological subdivision of DH, which was the largest subgroup in this series, is shown in Table 6. Although the incidence of CR was rather high and almost superimposable in all subgroups (except in two cases with centrocytic large), only about one-third of the cases were free from relapse at 5 yr. The lowest RFS was observed in the centroblastic and G subgroups, whereas all cases with H or immunoblastic histology and free from relapse at 2 yr remained persistently free of disease. The real difference within the DH subgroup can be clearly deduced by analysis of the 5-yr survival curves, which showed the different prognosis between subgroups G and H of the working formulation (Fig. 2) and between subgroups centroblastic and immunoblastic of the Kiel classification (Fig. 3). The apparent discrepancy between relatively low relapse and low survival rates for group G (and centroblastic) compared to group H (and immunoblastic) is explained by the fact that patients who did not achieve a CR had a median survival of 16.5 months in group G and 9 months in group H. However, 43% of patients who did not achieve a CR in group G were still alive at 5 yr, whereas all patients who did not achieve a CR in group H died within 15 months.

Table 6. Complete response (%) and 5-yr relapse-free survival (RFS) in the DH *subgroup of the Rappaport classification using the two other classifications*

Classification and subgroups		CR	RFS
R	DH	62.9	34.9
W.F.	G	63.3	31.9
	H	60.0	42.9
K	CB	65.4	28.2
	IB	57.1	34.1

DISCUSSION

In this case series, which is homogeneous for stage, systemic treatment and age, the use of the working formulation clearly identified three

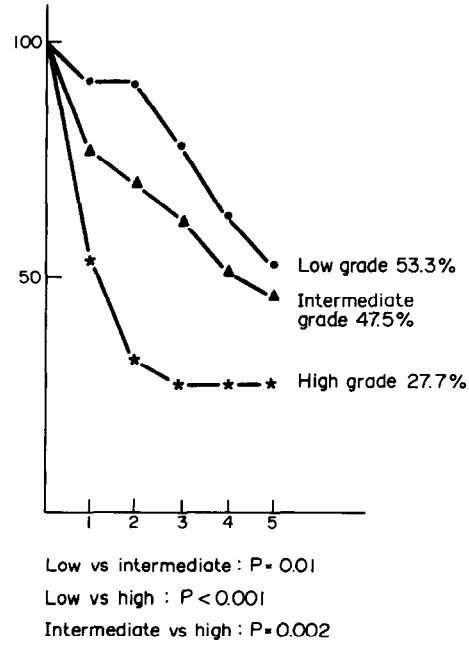

Fig. 1. Actuarial overall survival according to the prognostic subgroups of the working formulation (low vs intermediate: P = 0.01; *low vs high:* P < 0.001; *intermediate vs high:* P = 0.002).

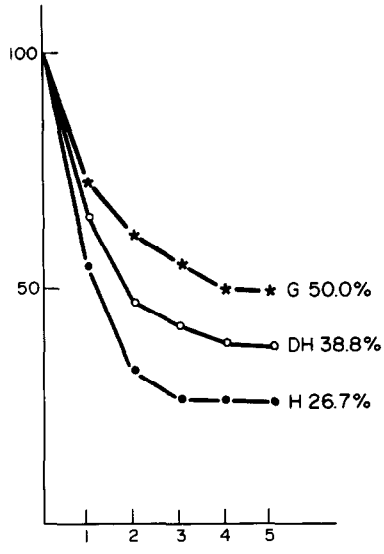

Fig. 2. Actuarial overall survival within DH lymphoma according to the working formulation (G vs H: P = 0.06).

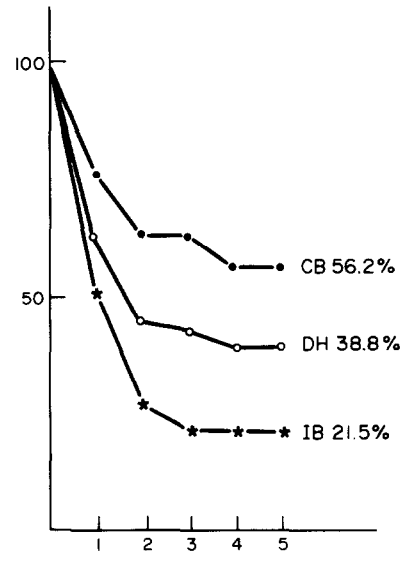

Fig. 3. Actuarial overall survival within DH lymphoma according to the Kiel classification (CB vs IB: P = 0.06).

different prognostic subgroups. Although the working formulation failed to indicate a relationship between achievement and duration of CR and prognostic subtypes of NHL (as did the other two classifications), overall survival, which is the most important parameter, confirmed different results for low-, intermediate- and high-grade histology. In fact, it is well known to the medical oncologist that a number of cases of NHL do not fit in any category if only a simple distinction between groups with good and poor prognosis is made, since they have a clinical course that runs in between. The possibility of reporting overall results of combination chemotherapy in three different groups instead of two can thus be considered a step forward in this complex field of pathology.

The group termed as intermediate of the working formulation comprises almost as many cases of the low- plus the high-grade malignancies of the present series. It therefore appears to be a definite category in terms of dimensions. This group, aside from the aforementioned considerations on overall survival, has prognostic relevance, if one also considers that in the present series there was a clear distinction among low-, intermediate- and high-grade malignancies as far as systemic symptoms and bulkiness of the disease are concerned. This is also true for the Kiel and to a lesser extent for the Rappaport classification; however, the latter recognizes only part of the low-grade NHL, whereas the former potentially incorporates those entities of intermediate grade that have already been identified on the basis of cell kinetic data [23]. For patients with advanced NHL treated with combination chemotherapy, the subdivision in three different groups makes sense and is therefore of definite clinical usefulness for the time being, since special chemotherapy schemes for each clinicopathological entity as listed (e.g. in the Kiel classification) are not available.

Our cases series also confirms that all three classifications allow the identification, within the unfavorable prognosis groups, of the subgroups that have the highest incidence of constitutional symptoms and bulky disease, such as DH (Rappaport), G and H (working formulation) and centroblastic and immunoblastic (Kiel). Within the unfavorable histology of the Rappaport classification, advanced DH has been indicated as a potentially curable disease by means of combination chemotherapy [24]. However, different long-term results have been reported in several series [24–30]. Since in most case series the Rappaport classification has been used, some differences might be attributed to the lack of distinction among the different subtypes grouped within the DH pattern. In our series the poor prognosis of the subgroup H was definitely different from that of G of the working formulation, as also appears from the Kiel classification, with a distinction between centroblastic and immunoblastic, as reported by other authors [31]. This difference in the 5-yr results could not have become apparent if only one group such as DH had been used for histological typing, and it may support the hypothesis that the different results in the various series could be attributed to a different composition of the various subgroups within the DH histology and not only to unequally efficacious treatment regimens.

Controversial answers have been given to the

question about the identification of the subgroups of patients with a good prognosis within DH histology. In particular, survival of patients of the large cleaved and noncleaved categories (included in group G of the working formulation) has been recently shown by Nathwani *et al.* [32] to be substantially superimposable, whereas in another earlier study at the National Cancer Institute (Bethesda, MD) the subgroup large cleaved was found to identify an excellent prognostic group [33]. In contrast, results from the University of Iowa showed that patients with large noncleaved lymphomas had significantly longer survival [24, 35]. The subdivision of DH lymphoma between the two groups G and H does not imply an oversimplification, since it is now rather clear that within category G large cleaved and large noncleaved cell NHL have a similar prognosis.

In fact, in recent years the question has been raised as to whether initial treatment in patients with advanced NHL is necessary in relatively asymptomatic cases, and whether intensive combination chemotherapy is indicated in patients with favorable histological types. In contrast, in patients with unfavorable histology, further effort has been made to intensify the number and doses of drugs in an attempt to improve the present cure rate [28–30] at the expense of an increased toxicity. This clearly means that the time has come when chemotherapy will have to be shaped and modulated according to the histological types. For this clinical purpose the working formulation could be useful to indicate (1) cases that do not require initial intensive treatment (single agents); (2) cases to be approached with conventional combination chemotherapy; and (3) cases to be treated on a clinical research basis with new intensive combinations.

In conclusion, the working formulation can be fruitfully used in patients with NHL treated with combination chemotherapy to analyze the response to treatment and to plan the administration of chemotherapy. If other case series of advanced NHL treated with combination chemotherapy are classified or reclassified according to this system and the results obtained compared with those obtained by us, it may be possible to better state analogies and overcome discrepancies in therapeutic results that are often attributable to the multiplicity of the existent classifications.

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