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The significance of the number of centroblasts in centroblastic/centrocytic lymphomas

A long term study in a large group of patients

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Summary. A group of 385 centroblastic/centrocytic lymphomas with long follow-up periods was subdivided on the basis of the relative number of centroblasts in the initial biopsies. Only minor differences in overall survival were found although a different survival pattern was observed between the groups. The transition into a high-grade malignant secondary centroblastic lymphoma correlated, at a statistically significant level, with the relative number of centroblasts in the initial biopsy.

Key words: Centroblastic/centrocytic lymphoma – Number of centroblasts – Secondary centroblastic lymphoma

Introduction

In the Kiel-classification of malignant lymphomas (Lennert 1978, 1981) those derived from follicular center cells (FCC) are divided into 3 groups. Malignant lymphoma (ML) centroblastic and ML centrocytic are composed of a "pure" proliferation of centroblasts and centrocytes, respectively and ML centroblastic/centrocytic of a combined proliferation of both cell types. In the latter group, however, the relative contribution of each cell type may vary considerably.

In the "working formulation" (WF; Rosenberg et al. 1982), on the other hand, the relative number of small and large cells is taken into account and hardly the cell types. Previous studies (Molenaar et al. 1983; v.d. Berg et al. 1983) in a small group of patients suggested that the relative numbers of centrocytes and centroblasts in ML centroblastic/centrocytic, correlate with histological and clinical characteristics. Subdivision of a large group of FCC lymphomas according to the WF (Molenaar et al. 1984) did not lead to significant differences between the groups. However, as mentioned above, cell size and not cell type was used as a criterion. Therefore, the

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present study focuses on those cases of this large group which are composed of a mixture of small centrocytes and centroblasts and which were subdivided on the basis of the relative number of centroblasts (Molenaar et al. 1983).

Material and methods

A group of 385 lymphomas was selected on the basis of (a) a diagnosis of ML centroblastic/centrocytic, made at the Lymph Node Registry in Kiel between 1953 and 1978, (b) the availability of paraffin sections of good quality, (c) a (partly) follicular growth pattern and (d) the availability of clinical data. These cases were subdivided as follows. Group SCC consisted of cases with a strong predominance of small centrocytes with sporadic centroblasts. In group CBCC/A centroblasts were easily found among the centrocytes and in group CBCC/B many centroblasts were present, often in clusters (for details: Molenaar et al. 1983).

All data concerning classification, growth pattern, sclerosis, age and sex of patients, initial or follow-up biopsy, follow-up period and eventual death of the patient were computerized. Most of the statistical analyses and the survival curves were processed automatically (SPSS program for survival, 1981). The survival periods were calculated from the date of the histological diagnosis till the patient's death or the last date of information. The follow-up period of the live patients ranged from 2 to 312 months (median 68). In 51 patients follow-up biopsies were performed, adding up to 60 biopsies.

Results

Cytological classification. Among the initial biopsies 144 were classified in group SCC, 145 in group CBCC/A and 96 in group CBCC/B (Table 1).

Histological variables (Table 1). All 3 groups showed a predominantly follicular growth pattern. Sclerosis occurred in 31% of the cases roughly equally distributed throughout the 3 groups.

Age and sex of the patients (Table 1). In all 3 groups a female preponderance was found. No differences in age or sex distribution were found between the 3 groups.

Survival. Actuarial survival curves were computed for the 3 cytological groups and in each of them for different growth patterns and presence

Table 1. Histological parameters and patients' data

Group	*n* (%)	Growth		Sclerosis		Sex		Age (mean)		
		F	F + D	+	−	M	F	all	M	F
SCC	144 (37.4)	92 (64)	52 (36)	42 (29)	102 (71)	67 (46)	77 (53)	55.4	54.6	54.4
CBCC/A	145 (37.7)	105 (72)	40 (28)	51 (35)	94 (65)	64 (44)	82 (56)	54.2	52.2	55.7
CBCC/B	96 (24.9)	61 (63)	35 (37)	25 (26)	71 (74)	34 (36)	61 (64)	56.9	52.5	59.3
Total	385 (100)	258 (67)	127 (33)	118 (31)	267 (69)	165 (43)	220 (57)	55.3	53.2	56.2

F: follicular, D: diffuse, M: male, F: female

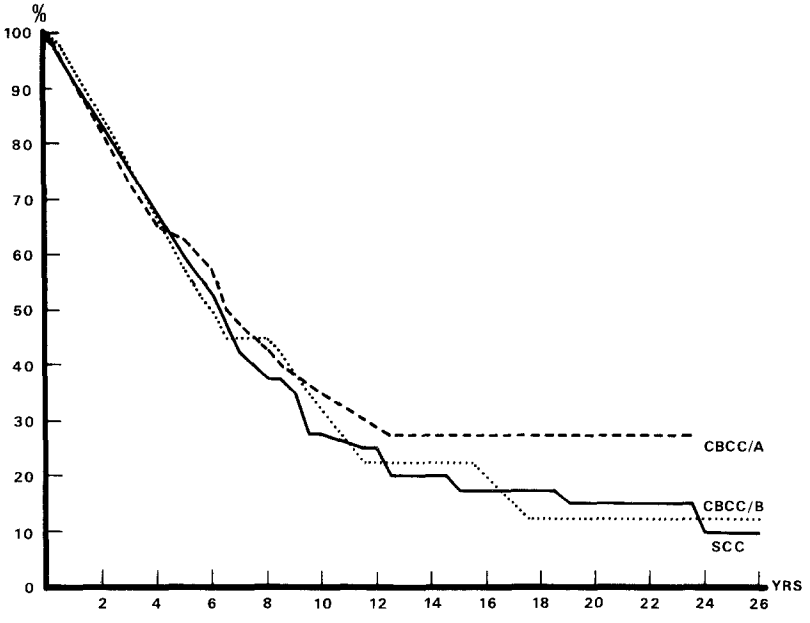

Fig. 1. Survival curves in the 3 cytological groups (for abbreviations: see text)

Table 2. Survival

Parameter	Group		(*n*)	Median (mths)	5. years (%)	10 years (%)	*P* Overall survival
A. Cytology	SCC		(144)	66	58	25	
	CBCC/A		(145)	70	63	30	
	CBCC/B		(96)	66	60	24	
B. Growth pattern	SCC,	F	(92)	70	62	27	0.012
		F + D	(52)	56	40	13	
	CBCC/A,	F	(105)	61	51	31	0.872
		F + D	(40)	82	61	39	
	CBCC/B,	F	(61)	57	47	18	0.924
		F + D	(35)	63	53	33	
C. Sclerosis	SCC,	+	(42)	45	47	32	0.366
		−	(102)	61	55	23	
	CBCC/A,	+	(51)	73	56	30	0.688
		−	(94)	64	62	30	
	CBCC/B,	+	(25)	92	63	39	0.118
		−	(71)	53	46	15	

F: follicular; D: diffuse. SCC, CBCC/A, B: see text

or absence of sclerosis. It appeared that the overall survival was not significantly different between the 3 groups. However, after 4 to 5 years the survival in group CBCC/A seems to be better than in the other 2 groups (Fig. 1). The growth pattern appeared to have a significant influence on survival

Table 3. Follow-up biopsies

Primary		Follow-up				
		SCC	CBCC/A	CBCC/B	sec. CB	
SCC	(144)	6	4	2	3	15
CBCC/A	(145)	4	8	6	7	25
CBCC/B	(96)	1	5	6	8	20
Total	(385)	11	17	14	18	60

only in group SCC, such that a follicular growth pattern was more favourable than a follicular and diffuse growth (Table 2). Sclerosis had no significant influence on survival (Table 2).

Follow-up material. Sixty follow-up biopsies from 51 patients were obtained (Table 3), 42 of which again were diagnosed as ML centroblastic/centrocytic. In 18 patients, including 3 in which earlier follow-up biopsies revealed a centroblastic/centrocytic lymphoma, a secondary centroblastic lymphoma was diagnosed, i.e. in 3 cases of group SCC (2.08%), in 7 of group CBCC/A (4.8%) and in 8 of group CBCC/B (8.3%). The period between the initial biopsy and the one demonstrating a centroblastic lymphoma ranged from 1 to 132 months (mean 51, median 47). The differences in frequency between the 3 groups appeared statistically significant (Chi-square, $p<0.05$), but the time lapse was roughly similar.

Discussion

The purpose of the current study was to test in a large group of patients with long follow-up the validity of a previously proposed cytological subdivision of CBCC lymphomas (Molenaar et al. 1983; v.d. Berg et al. 1983). It was not meant to introduce a new classification, but merely to elucidate the role of centroblasts in follicular CBCC lymphomas of the Kiel-classification (Lennert 1978 and 1981). In order to facilitate the interpretation of the current results for readers not familiar with the latter classification a comparison with some major classifications has been given in table 4. The current findings on histological and epidemiological variables largely confirm those in previous papers (Molenaar et al. 1983; v.d. Berg et al. 1983) to which is referred for a detailed discussion in relation to earlier studies. Briefly, a follicular growth pattern was more common than a follicular and diffuse growth, female patients predominated and the majority of the patients was in the 6th decade of life. No differences were found between the 3 subgroups.

In the evaluation of the survival curves the clinical stage at presentation was not taken into consideration. However, it has been reported (Jones et al. 1973; Patchefsky et al. 1974; Mann et al. 1979; Stein et al. 1979; Aine

Table 4. Comparison of the current subclassification with major classifications

Group	Working formulation	Rappaport[a]	Lukes and Collins[b]	Kiel
SCC	FSC	PDL	small cleaved FCC	(ML centrocytic) ML centroblastic/centrocytic
CBCC/A	FSC	MH	small cleaved FCC	ML centroblastic/centrocytic
CBCC/B	FSC FM	MH	small cleaved FCC	ML centroblastic/centrocytic

FSC: follicular small cleaved; FM: follicular mixed; FL: follicular large cell; PDL: poorly differentiated lymphocytic; MH: mixed histiocytic lymphocytic; FCC: follicle center cells; ML: malignant lymphoma

[a] 1966 [b] 1974

et al. 1982; Rosenberg et al. 1972; vd Berg et al. 1983) that in follicular lymphomas advanced clinical stages does not correlate with poor survival.

Due to the wide geographical area from which the material was derived and the long follow-up, the treatment was diverse, but most patients were treated before modern regimens were established, which results in a relatively "natural" course of the disease. Finally, the large number of patients and the long follow-up should be emphasized, which give reliable information. Although no significant differences were found in overall survival, different behaviour was observed at different time intervals following the diagnosis. Thus, in all 3 groups (SCC, CBCC/A and B) a roughly similar survival was found in the first 4 to 5 years, but thereafter the survival in group CBCC/B with many centroblasts was worse than in group CBCC/A with less centroblasts. The finding of a poorer survival in group SCC with very few centroblasts seems remarkable, but was also reported for poorly differentiated lymphocytic (PDL) lymphomas as compared to mixed histiocytic (MH) lymphomas (Mann et al. 1979). Group SCC appears to be at the border between ML centroblastic/centrocytic and ML centrocytic, the latter of which has a poorer survival (Lennert 1978, and 1981). In this concept cases with an extensive diffuse component are even closer to ML centrocytic, which shows a predominantly diffuse growth (Lennert 1978, and 1981) and, indeed, group SCC is the only group in which follicular and diffuse cases have a significantly poorer survival than entirely follicular cases. Moreover, if the entirely follicular cases in group SCC are compared with those in groups CBCC/A and B, both the median and 5-year survival is better. These findings correspond to those of Patchefsky et al. (1974), who demonstrated a better survival for PDL lymphomas with a high degree of nodularity than both PDL lymphomas with minor nodularity and nodular MH lymphomas.

Transition into a high grade malignant lymphoma occurred statistically more frequently in groups with a relatively high number of centroblasts in the initial biopsy, in keeping with the findings of Risdall et al. (1979) and of Hubbard et al. (1982). A subdivision of the same group of patients

according to the "working formulation" (Rosenberg et al. 1982) did not result in a statistical significance between the follicular, small cleaved (FSC) group and the follicular mixed (FM) group (Molenaar et al. 1984) in this respect.

Conclusion. The findings in the current group of patients with CBCC lymphomas with a relatively "natural" course of the disease suggest that the number of centroblasts correlates with differences in survival. In particular, a high number of centroblasts in the initial biopsy correlates at a statistically significant level with the development of a secondary centroblastic lymphoma. Therefore, especially in such cases, primary therapy should be aimed at an initial complete response rate, which gives better chances for survival than a partial or minimal response (Cabanillas et al. 1979; Herrmann et al. 1982) and may prevent a rapid fatal course after development of a secondary centroblastic lymphoma.

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References

Aine R, Alavaikko M, Kataja M (1982) The Lukes and Collins classification of non-Hodgkin's lymphomas. 2. A survival study of 301 patients. Acta Pathol Microbiol Immunol Scand Sect A 90:251–256

Cabanillas F, Smith T, Bodey GP, Gutterman JU, Freireich EJ (1979) Nodular malignant lymphomas. Factors affecting complete response rate and survival. Cancer 44:1983–1990

Herrmann R, Barcos M, Stutzman L, Walsh D, Freeman A, Sokal J, Henderson ES (1982) The influence of histologic type on the incidence and duration of response in non-Hodgkin's lymphoma. Cancer 49:314–323

Hubbard SM, Chabner BA, de Vita DT, Simon R, Berard CW, Jones RB, Garvin AJ, Canellos GP, Osborne K, Young RC (1982) Histologic progression in non-Hodgkin's lymphoma. Blood 59:258–264

Jones SE, Fuks Z, Bull M, Kadin ME, Dorfman RF, Kaplan HS, Rosenberg SA, Kim H (1973) Non-Hodgkin's lymphomas. IV Clinicopathologic correlation in 405 cases. Cancer 31:806–823

Lennert K (1978) Malignant lymphomas other than Hodgkin's disease. Histology, cytology, ultrastructure, immunology. Springer Verlag, Berlin Heidelberg New York

Lennert K (1981) Histopathology of non-Hodgkin's lymphomas. Springer, Berlin, Heidelberg New York

Lukes RJ, Collins RD (1974) Immunologic characterization of human malignant lymphomas. Cancer 34:1488–1503

Mann RB, Jaffe ES, Berard CW (1979) Malignant lymphomas – a conceptual understanding of morphologic diversity. Am J Pathol 94:105–193

Molenaar WM, Bartels H, Koudstaal J (1984) Histological, epidemiological and clinical aspects of centroblastic-centrocytic lymphomas subdivided according to the "working formulation". Br J Cancer 49:263–268

Molenaar WM, van den Berg HM, Halie MR, Poppema S (1983) The heterogeneity of follicular center cell lymphomas. I. Cytohistological, immunological and enzymehistochemical aspects. Cancer 52:2269–2276

Patchefsky AS, Brodovsky HS, Menduke H, Southard M, Brooks J, Nicklas D, Hoch WS

(1974) Non-Hodgkin's lymphomas: a clinicopathologic study of 293 cases. Cancer 34:1173–1186

Rappaport H (1966) Atlas of tumor pathology. Tumors of the hematopoietic system. Washington DC, Armed Forces Inst Pathol

Risdall R, Hoppe RT, Warnke R (1979) Non-Hodgkin's lymphoma: a study of the evolution of the disease based upon 92 autopsied cases. Cancer 44:529–543

Rosenberg SA et al. (1982) National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Cancer 49:2112–2135

SPSS update 7–9 New Procedures and facilities for releases 7–9. (1981) McGraw-Hill Book Company, Chicago, Hull CH, Nie MH (eds)

Stein RS, Cousar J, Flexner JM, Graber SE, McKee LC, Krantz S, Collins RD (1979) Malignant lymphomas of follicular center cell origin in man. III Prognostic features. Cancer 44:2236–2243

Van den Berg HM, Molenaar WM, Poppema S, Halie MR (1983) The heterogeneity of follicular follicle center cell tumors. II Clinical follow-up of 30 patients. Cancer 52:2264–2268

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