Pergamon

European Journal of Cancer, Vol. 34, No. 3, pp. 329–336, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10056-9

Original Paper

Mantle Cell Lymphoma: Clinical Features, Treatment and Prognosis of 94 Patients

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Mantle cell lymphoma (MCL) is a subtype of B-cell non-Hodgkin's lymphoma recently recognised as a distinct disease entity. Little is known about the prognostic factors and optimal treatment of MCL. The aim of this study was to analyse retrospectively the clinical features and effect of treatment in 94 MCL patients diagnosed and treated in one centre between 1980 and 1996, and to find out different factors influencing the treatment results and prognosis. The median age of the patients was 66 years, and 77% were over 60 years old. Of the patients, 76% had advanced disease, the performance status (PS) was WHO 0–1 in 86%, and B symptoms were present in 35% of the cases. Bone marrow infiltration was found in 61% and overt leukaemia in 12% of the patients. Of the patients, 47% achieved complete remission with first- or second-line therapy. The median duration of remission, time to treatment failure (TTF), and survival were 28, 18, and 41 months, respectively. In multivariate analyses, age, stage and leukaemic disease were significantly associated with TTF, and age, stage, leukaemic disease and lactate dehydrogenase (LDH) with survival. Long-term prognosis is poor in MCL. None of the conventional chemotherapies seems curative. A prospective randomised trial should be made to evaluate the benefit of anthracycline-containing regimens in MCL.

Key words: mantle cell lymphoma, non-Hodgkin's lymphoma, diagnosis, treatment, prognosis, International Prognostic Index
Eur J Cancer, Vol. 34, No. 3, pp. 329–336, 1998

INTRODUCTION

MANTLE CELL lymphoma (MCL) is a recently well-characterised subtype of B-cell non-Hodgkin's lymphoma estimated to represent between 2 and 9% of all non-Hodgkin's lymphomas [1, 2]. Previously defined subtypes, being variously termed as intermediate lymphocytic lymphoma, mantle zone lymphoma and centrocytic lymphoma, have now been considered to comprise a single disease entity and in 1992 the unification of all these terms under the name mantle cell lymphoma was proposed [3].

MCL is distinguished from other non-Hodgkin's lymphomas by morphological, cytochemical, immunohistochemical and cytogenetic studies. It is composed of small or intermediate lymphatic cells with cleaved nuclei. They express B-cell associated antigens, surface immunoglobulins IgM and IgD, and CD5, but are usually negative for CD10 and CD23 antigens [4–6]. The characteristic cytogenetic abnormality is a t(11;14)(q13;q32) translocation with re-arrangement of the *bcl1/CCND1* gene found in 50–70% of MCLs [7, 8]. The *CCND1* gene encodes for cyclin D1 protein. Its overexpression is seen in nearly all cases of MCL, and antibody to cyclin D1 is shown to be highly sensitive and specific for MCL [9].

According to the Kiel Classification, MCL (identified as centrocytic lymphoma) belongs to low-grade lymphomas. However, in spite of its indolent histological features, MCL is known to have a poorer prognosis than other small-cell lymphomas. The survival time is short and the survival curves do not show any evidence of cure [3, 10, 11]. In the widely used Working Formulation classification, MCL is not recognised as a distinct disease entity, but has been included in a subgroup of diffuse small cleaved cell or diffuse mixed small and large cell lymphomas of intermediate grade of malignancy or

classification, several lymphoma entities, including MCL, have a range of morphological grade [5]. Little information is available about the prognostic factors and optimal treatment of MCL. Whether anthracycline-containing chemotherapy improves the prognosis or not is still unclear [13, 14].

The purpose of this study was to analyse the clinical features and effect of treatment in MCL patients and to find out different factors influencing the treatment results and prognosis. The role of the International Prognostic Index (IPI) [15] in predicting the prognosis in MCL was particularly evaluated.

PATIENTS AND METHODS

Patients

A retrospective study of 94 patients with MCL diagnosed and treated from November 1980 to April 1996 was undertaken. The median follow-up for all patients was 78 months (range 6–198 months) and for the surviving patients 51 months (range 6–129 months). Patients with diffuse centrocytic lymphoma, according to the Kiel Classification, or MCL were collected from a computer database. The pathology specimens were reviewed by one of the authors (K.F.), and only the patients with a confirmed diagnosis of MCL according to the recently updated criteria (REAL) [5] were included. All 94 patients met strict morphological criteria of MCL. Immunohistochemistry was performed on frozen tissue biopsies from 71 patients and on paraffin-embedded biopsies from 23 patients. In the frozen tissue sections the lymphomas of 71/71 patients were CD20 and/or CD19+, 64/64 were IgM+, 48/57 were IgD+, 34/71 were kappa+, 37/71 were lambda+ and 55/55 were CD2−. In paraffin-embedded sections, all cases were CD20/L26 positive and CD3 negative; 70/82 were CD5 positive (52/59 stained in frozen tissue sections and 18/23 in paraffin-embedded sections). Sixty stained cases were cyclin D1 (NCL-Cyclin D1-GM, Novocastra, Newcastle, U.K.) positive in paraffin-embedded sections. No difference in remission rate, time to treatment failure (TTF) or survival were seen in 73 cases with positive cyclin D1 and/or CD5+IgD expression or in 21 cases without known positive cyclin D1 or CD5+IgD expression.

The clinical features evaluated for potential prognostic importance were age, sex, performance status (PS), Ann Arbor stage, B symptoms, IPI, size of the largest tumour, sites of lymphomatous involvement and the number of extra nodal disease sites. In addition, a number of laboratory findings at the time of diagnosis were assembled.

The stage of the disease was assessed by clinical evaluation combined with thorax X-ray examination, thoracic, abdominal and pelvic computed tomography (CT) scans and bone marrow aspirate and biopsy. At the time of diagnosis, a bone marrow biopsy was taken in all but 4 patients. In 5 of the examined 90 cases, the bone marrow biopsy specimens were non-diagnostic for technical reasons. Gastrointestinal tract involvement of the symptomatic patients was detected by endoscopic examinations or laparotomy. Other known or suspected extra nodal disease was investigated by CT or with other appropriate imaging techniques. Biopsies were performed to confirm the involvement of extra nodal sites.

PS was assessed according to the WHO criteria [16]. The Ann Arbor stage was designated according to Lister and associates [17]. The largest dimension of the largest site of bulky disease was measured and reported as being <10 cm, recorded as ≤ 1 or >1. Spleen and Waldeyer's ring were classified as nodal sites. The patients were classified retrospectively to four risk groups according to IPI, a recently proposed model to predict the outcome in patients with large-cell lymphomas based on patients' clinical characteristics (i.e. age, Ann Arbor stage, PS, number of extra nodal sites, serum lactate dehydrogenase (LDH) level) at presentation [15].

Treatments

First-line therapy. 5 patients had no treatment for their lymphoma. 8 of the 23 patients with stage I or II disease were operated on or treated with local radiotherapy only. Chlorambucil with or without prednisone, or CVP (cyclophosphamide, vincristine, prednisone) was given to 19 patients. The other patients received more intensive regimens: 59 patients received chemotherapy, including anthracyclines [M-BACOD (high-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone with or without bleomycin) or CNOP (mitoxantrone instead of doxorubicin)], and 3 patients received ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). 4 of the patients with advanced disease were also irradiated or operated on in addition to chemotherapy.

Consolidation therapy. 15 of the patients who achieved remission following first-line therapy were given further therapy for consolidation: radiotherapy ($n=8$), radiotherapy and chlorambucil ($n=1$), radiotherapy and CHOP ($n=1$), chlorambucil ($n=2$), M-BACOD ($n=2$) or low-dose CHOP ($n=1$).

Second-line therapy. An additional therapy given to the patients without satisfactory response to first-line therapy was defined as second-line therapy. It was divided into three groups: (1) local treatment (operation or radiotherapy); (2) chlorambucil (with or without radiotherapy, prednisone or interferon) or CVP; and (3) more intensive combination chemotherapy.

Assessment of response

Complete response (CR) was defined as total disappearance of all clinical evidence of the disease and normalisation of the radiographic results and biopsy of the bone marrow which had been abnormal before treatment. Regression of at least 50% of all measurable disease was defined as a partial response (PR). Relapse was defined as the reappearance of malignant lymphoma in a patient who had previously had a complete remission. The duration of remission was defined as the time from the documentation of a complete remission to relapse. Progression was defined as relapse, increase of tumour size or appearance of a new tumour. TTF was defined as survival from the date of diagnosis to progression of the lymphoma, to the death of any cause, or to the last follow-up [18]. The patients without progression were censored at the date of the last follow-up. Survival was measured as the interval between the date of diagnosis and death or the last follow-up evaluation. The patients alive at the time of the last follow-up were censored for survival.

Statistical methods

The analyses were performed on a VAX 6000 computer using BMDP statistical software package (BMDP Statistical

association between remission and individual clinical features was analysed using the chi-square test and Fisher's exact test. The duration of remission, TTF and overall survival were estimated by the method of Kaplan and Meier. The univariate association between TTF or overall survival and individual clinical features was determined using the Mantel–Cox test and generalised Wilcoxon test. To discover the independence of the different prognostic factors, Cox's proportional hazards regression model and logistic regression were used. The variables chosen for the multivariate analyses were age, haemoglobin level, leucocyte count, lymphocyte count, erythrocyte sedimentation rate, LDH (as continuous variables), sex, stage (I–II versus III–IV), B symptoms (absent or present), PS (WHO 0 versus 1–4), bone marrow infiltration, leukaemic disease, involvement of spleen and first-line treatment (others versus anthracycline-containing regimens and ESHAP). In addition, five IPI variables, as defined in the international non-Hodgkin's lymphoma prognostic project (age ≤ 60 versus > 60 years, stage I–II versus III–IV, PS 0–1 versus 2–4, LDH normal versus elevated) [15], were analysed together in multivariate analyses. All significance values were calculated from two-sided tests.

RESULTS

Clinical features

At the time of diagnosis, 72 of the 94 patients (77%) were over 60 years old with a median age of 66 years (range 44–87 years). Fifty-nine per cent of the patients were males. The clinical characteristics of the patients are summarised in Table 1. The PS of the patients was usually good (WHO 0–1 in 86%). Most patients had an advanced stage disease (76% had Ann Arbor stage III or IV), but only 35% of the patients had B symptoms. Bulky tumours were rare and 40% of the patients had more than one extra nodal site of disease. Bone marrow involvement was found in 61%, but leukaemic disease in only 12% of the patients. Spleen, gastrointestinal tract and Waldeyer's ring were the other most common sites of lymphomatous involvement. IPI was evaluable in 83 patients (88%). In 11 cases, either the LDH value and/or the number of extra nodal sites at diagnosis were unknown. The patients were almost equally distributed among low, low–intermediate, high–intermediate and high risk groups according to IPI.

Table 1. Characteristics of 94 patients with mantle cell lymphoma at the time of diagnosis

Parameter	*n*	%
Performance status (WHO)		
0	38	40
1	43	46
2	9	10
3	2	2
4	2	2
Ann Arbor stage		
I	13	14
II	10	11
III	7	7
IV	64	68
B symptoms		
Absent	61	65
Present	33	35
International Prognostic Index ($n = 83$)		
Low	19	23
Low–intermediate	24	29
High–intermediate	22	27
High	18	22
Dimension of the largest tumour		
< 10 cm	75	80
≥ 10 cm	19	20
Extranodal involvement ($n = 89$)		
≤ 1 site	53	60
> 1 site	36	40
Site of disease		
Bone marrow ($n = 85$)	52	61
Blood	11	12
Spleen	29	31
Gastrointestinal tract	18	19
Conjunctiva/orbita	6	6
Waldeyer's ring	16	17
Lactate dehydrogenase ($n = 86$)*		
< 450 U/l	53	62
≥ 450 U/l	33	38
Thymidine kinase ($n = 46$)†		
< 5 U/l	15	33
≥ 5 U/l	31	67

*Normal value < 450 U/l. †Normal value < 5 U/l.

Outcome of the patients

Remissions. There were 5 elderly patients who received no active treatment for their lymphoma due to their poor condition at diagnosis. None of them showed spontaneous recovery. Of the other 89 patients, first-line therapy resulted in CR in 34% (30/89) and PR in 44% (39/89). No response was seen in 15% (13/89) and progressive disease in 7% (6/89) of the patients. 1 patient died during first-line therapy. The effects of different treatments are given in Table 2.

All 5 patients who achieved CR by operation had stage I disease. Of the 19 patients treated with chlorambucil or CVP only 2 (11%) achieved CR, whereas 21 of the 62 patients (34%) treated with anthracycline-containing regimens or ESHAP achieved CR ($P = 0.048$). Of the 59 patients who did not achieve CR with the first-line therapy, 14 (24%) achieved it with the second-line therapy. Radiotherapy was given to 5 of them, 8 received chemotherapy (2 chlorambucil, 6 combi-

Table 2. Complete remissions with first-line therapy

Treatment group	Complete remissions	
	n	(%)
Operation	5/5	(100)
Radiotherapy	2/3	(67)
Chlorambucil ± prednisone	1/13	(8)
CVP	1/6	(17)
M-BACOD	11/27	(41)
CHOP/CNOP	9/32	(28)
ESHAP	1/3	(33)
Total	30/89	(34)

CVP, cyclophosphamide, vincristine, prednisone; M-BACOD, high-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone with or without bleomycin; CNOP, as CHOP

CR was achieved by 44 patients (47% of all 94 or 49% of those 89 patients whose treatment was evaluable). 23 of the 44 complete responders (52%) relapsed during follow-up. The median duration of remission was 28 months (95% confidence interval (CI) 14–57 months) and 44% of the patients were in remission at 3 and 25% at 5 years. No plateau was observed in the curve. The second remission, usually short in duration, was achieved in 14 cases (61%), 12 with chemotherapy and 2 with radiotherapy.

The clinical findings at presentation and their association with the remission rate in the univariate analysis are shown in Table 3. A low remission rate was highly associated with poor PS ($P = 0.002$), advanced stage ($P < 0.001$), B symptoms ($P < 0.001$), high IPI ($P = 0.004$), bone marrow infiltration ($P < 0.001$), leukaemic disease ($P = 0.015$), low haemoglobin level ($P = 0.002$), leucocytosis ($P = 0.002$), low platelet count ($P = 0.009$) and elevated LDH ($P = 0.003$) and thymidine kinase ($P = 0.004$) levels. The variables with statistically significant impact on the CR rate in the logistic regression analysis were first-line therapy, haemoglobin level, stage, sex and LDH level (Table 4).

Time to treatment failure (TTF). The median TTF was 18 months (95% CI 15–25 months). No plateau was observed in the curve (Figure 1). In the univariate analysis, the factors predicting a shorter TTF were age over 60 years, poor PS, advanced stage, B symptoms, high IPI, bone marrow infiltration, leukaemic disease, low haemoglobin level, leucocytosis and high LDH level (Table 5). The first-line treatment with anthracycline-containing regimens and ESHAP, compared to chlorambucil and CVP, was associated with a longer TTF ($P = 0.008$). In the multivariate analysis, leukaemic disease, stage and age were significantly associated with TTF (Table 4).

Overall survival. Survival was 54 and 28% at 3 and 5 years, respectively (median 41 months, 95% CI 28–55 months). No plateau in the survival curve was observed during the follow-up time (Figure 1). As shown in Table 5, age (Figure 2a), PS, stage (Figure 2b), B symptoms, bone marrow infiltration, leukaemic disease (Figure 2(c)), haemoglobin level, leucocytosis, erythrocyte sedimentation rate, LDH level (Figure 2d) and IPI (Figure 3) were found to have prognostic significance on survival in the univariate analysis. In addition, the use of anthracycline-containing regimens and ESHAP as the first-line therapy was associated with a longer survival (Figure 4). In Cox's proportional hazards regression model, age, leukaemic disease, LDH level and stage were found to be statistically significant prognostic factors (Table 4).

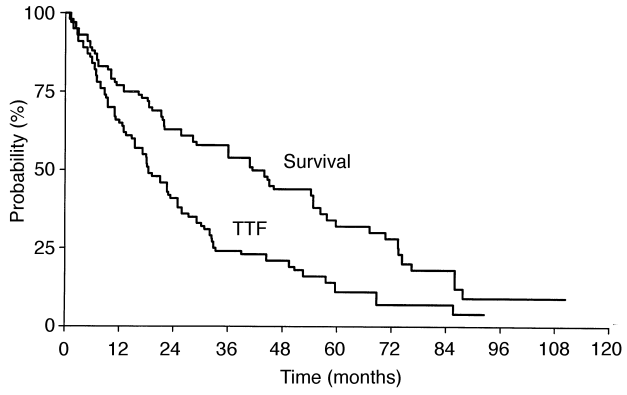

Figure 1. Time to treatment failure (TTF; median 18 months)

Table 3. Remission rates with the first- and second-line therapy of the 89 patients who received active treatment

Parameter	No. of patients	Remissions (CR) *n*	(%)	*P* value
Age				
≤ 60 years	22	14	(64)	
> 60 years	67	30	(45)	0.125
Sex				
Male	52	21	(40)	
Female	37	23	(62)	0.043
Performance status				
0	36	25	(69)	
1–4	53	19	(36)	0.002
Stage				
I–II	22	19	(86)	
III–IV	67	25	(37)	< 0.001
B symptoms				
Absent	56	36	(64)	
Present	33	8	(24)	< 0.001
International Prognostic Index ($n = 80$)				
Low	19	16	(84)	
Low-intermediate	23	12	(52)	
High–intermediate	22	9	(41)	
High	16	4	(25)	0.004
Site of disease				
Bone marrow ($n = 81$)				
Yes	50	17	(34)	
No	31	23	(74)	< 0.001
Blood				
Yes	10	1	(10)	
No	79	43	(54)	0.015
Spleen				
Yes	27	6	(22)	
No	62	38	(61)	0.001
Haemoglobin level ($n = 85$)				
≤ 125 g/l	43	14	(33)	
> 125 g/l	42	28	(67)	0.002
Leucocyte count ($n = 85$)				
$\leq 10 \times 10^9$/l	70	40	(57)	
$> 10 \times 10^9$/l	15	2	(13)	0.002
Platelet count ($n = 83$)				
$< 140 \times 10^9$/l	20	5	(25)	
$\geq 140 \times 10^9$/l	63	37	(59)	0.009
Lactate dehydrogenase ($n = 82$)				
< 450 U/l	51	32	(63)	
≥ 450 U/l	31	9	(29)	0.003
Thymidine kinase ($n = 43$)				
< 5 U/l	12	11	(92)	
≥ 5 U/l	31	14	(45)	0.004

IPI. Separately, five IPI variables (as defined in [15]) were analysed together in the multivariate analyses. Of these,

Table 4. Significant variables in logistic regression model and Cox's proportional hazards regression model

	Odds ratio	95% confidence interval	P value
Complete remission rate			
First-line therapy*	35.9	4.06–318	0.001
Haemogloblin level	11.1	2.15–57.0	0.004
Stage (I–II versus III–IV)	0.074	0.012–0.471	0.005
Sex	5.80	1.58–21.4	0.007
LDH level	0.995	0.990–0.999	0.018
	Relative risk	**95% confidence interval**	**P value**
Time to treatment failure			
Leukaemic disease	2.537	1.228–5.240	0.012
Stage (I–II versus III–IV)	2.185	1.118–4.269	0.022
Age	1.030	1.002–1.058	0.033
Survival			
Age	1.067	1.032–1.103	< 0.001
Leukaemic disease	3.152	1.478–6.723	0.003
LDH level	1.001	1.000–1.002	0.015
Stage (I–II versus III–IV)	2.179	1.018–4.666	0.046

*Others versus anthracycline-containing regimens and ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). LDH, lactate dehydrogenase.

DISCUSSION

Although MCL usually shows an indolent histology of low-grade lymphoma, an aggressive clinical course is common. The long-term prognosis is poor and no cure is reached with conventional chemotherapy in an advanced disease. No optimal treatment strategies have been defined, and whether the anthracycline-containing regimens improve the prognosis or not is still unclear [13, 14, 19].

The clinical characteristics of the present MCL patients support those found in previously published smaller series

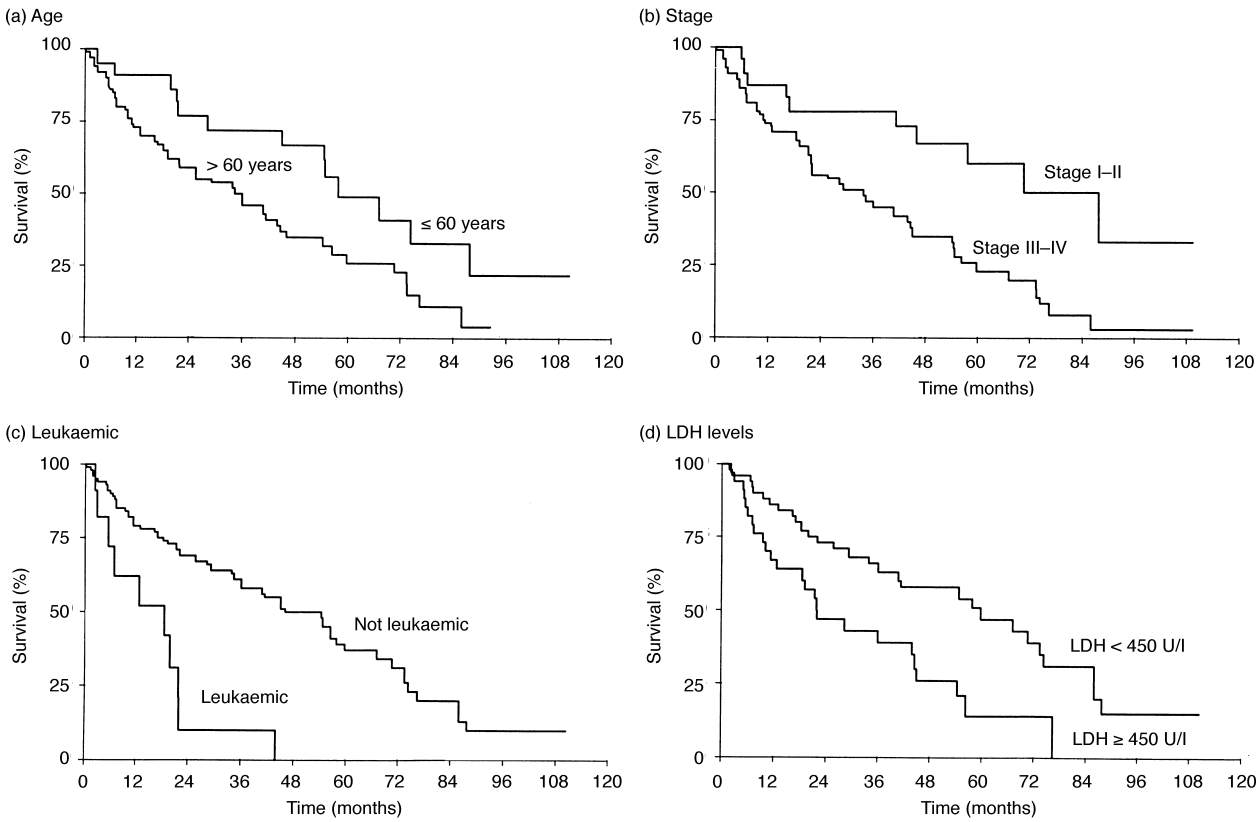

Figure 2. (a) Overall survival for 22 patients ≤ 60 years old compared to 72 patients > 60 years of age ($P = 0.014$). (b) Overall survival for 23 patients with stage I–II disease compared to 71 patients with stage III–IV disease ($P = 0.002$). (c) Overall survival for 83 patients without leukaemic disease compared to 11 patients with leukaemic disease ($P < 0.001$). (d) Overall survival for 53

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