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A Danish population-based analysis of 105 mantle cell lymphoma patients: incidences, clinical features, response, survival and prognostic factors

N.S. Andersen*, M.K. Jensen, P. de Nully Brown, C.H. Geisler

For The Danish Lymphoma Study Group, LYFO, Department of Hematology, Rigshospitalet, Copenhagen, Denmark

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Abstract

This study presents the first large clinical analysis of 105 unselected mantle cell lymphoma (MCL) patients diagnosed from 1992 to 2000 in a well-defined Danish population. The annual incidences were 0.7/100 000 for men and 0.2/100 000 for women, with no significant change during the study period. Of 97 evaluable cases, 43% achieved a complete response (CR) after initial therapy. The median disease-free (DFS) and overall survival (OS) rates were 15 and 30 months, respectively. In multivariate analysis, splenomegaly ($P=0.002$), anaemia ($P=0.0001$) and age ($P=0.002$), but not the international prognostic index (IPI) and the Ann Arbor staging system, had an independent impact on survival. Moreover, in a sub-analysis of 45 younger MCL patients (<65 years), a trend towards an OS plateau of 58% was observed in cases without splenomegaly and anaemia ($n=29$). Thus, in contrast to previously suggested prognostic factors, these variables may prove useful for clinical decisions in a significant subset of MCL patients.

Keywords: Mantle cell lymphoma; Population-based; Incidence; Clinical features; Survival; Prognosis

1. Introduction

In 1992, Banks and colleagues described cases of non-Hodgkin's lymphoma (NHL) with identical cytological features despite being classified in different low and intermediate NHL subgroups, and proposed the term mantle cell lymphoma (MCL) for these cases [1]. In the Working Formulation (WF), MCL cases were derived from WF A-E and were predominantly characterised as diffuse, small cleaved cell-lymphomas [1,2]. In contrast, the well-defined centrocytic lymphoma (CC) of the Kiel classification was regarded as identical to MCL [1,3]. Two years later, the Revised European-American Classification of Lymphoid Neoplasms (REAL) classification characterised MCL by distinct morphological, immunophenotypical and cytogenetical features, and the European Lymphoma Task Force (ELTF) workshop on MCL developed criteria for the diagnosis of MCL [4,5].

Previously, only one population-based study comprising 41 patients with MCL diagnosed between 1981 and 1989 has been reported [6]. This study and recent single institution-based series show a high rate of recurrences and poor long-term survival following conventional combination chemotherapy (CT) [7–11]. The NHL classification project analysed the prognostic significance of clinical and laboratory features as described by the international prognostic factor index (IPI) [7,12]. In contrast to other lymphoma subtypes of the REAL classification, the survival curves of the individual risk groups of the IPI were not significantly different in MCL [7]. In a large non population-based series of MCL, patient's age, lactate dehydrogenase (LDH) level, leukaemic MCL and advanced stage of disease had a significantly negative impact on survival [10]. However, defining the relative impact of the various prognostic factors are hampered by the lack of studies of large unselected series of patients from a well-defined population. Furthermore, in recent years the application of immunohistochemical markers combined with well-

* Corresponding author at: Department of Hematology L-4041, Rigshospitalet, Blegdamsvej 9, 2100 Kbh, Ø, Denmark Tel.: +45-3545-4045.

E-mail address: nanders@rh.dk (N.S. Andersen).

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defined morphological characteristics may help to identify MCL cases and reduce the frequency of misclassification [5]. The aim of the present study was to present incidence rates, clinicopathological features, survival and prognostic factors of the hitherto largest series of unselected MCL patients comprising 105 cases diagnosed in western Denmark during the period 1992–2000.

2. Patients and methods

2.1. Patients

A population-based registry, Danish Lymphoma Study Group Registry (LYFO), of all new cases of NHL in western Denmark (Jutland and Funen, 2.88 million inhabitants) was started on 1 January 1983 and is still ongoing. All hospitals and pathological laboratories in the region participated through a study group consisting of 18 specialists from the three main regional referral centres. As MCL was defined as a distinct lymphoma entity in 1992, we chose a study period from 1992 to the middle of 2000 in order to reduce misclassifications. We studied 122 consecutive cases.

2.1.1. Pathology

All patients had their diagnostic sample reviewed by the LYFO board of pathologists. From the start of the study period, all participating pathologists followed the Kiel (CC) and from 1994 the REAL (MCL) classification for subclassification of NHLs [3,4]. As inclusion criteria for this study, we applied the Annecy criteria on the pathology descriptions, as defined by the European Lymphoma Task Force. Briefly, the criteria state that in patients with a very typical cytology some deviation in immunophenotype could be accepted, but in patients with atypical cytology, immunophenotype must be typical. Cyclin D1 expression was useful, but not mandatory, for the diagnosis of MCL [5]. Here, the diagnosis of MCL/CC was based on a typical cytology in 97 of 122 MCL/CC cases registred in LYFO during the study period. In 8 cases, the cytology was not definitive, but a typical immunophenotype (CD20+/CD5+/CD23−) established the diagnosis of MCL. In 17 cases, the cytology and the immunophenotype were either not typical of MCL or not fully examined. Consequently, these cases were excluded. Thus, a total of 105 MCL/CC patients were included for further studies.

2.2. Immunohistochemistry

2.2.1. Antigens

CD19, CD20, CD5, CD23, Ki67 and cyclin D1 were detected using standard immunohistochemical staining. Cyclin D1 detection was only sporadically reported in this time period. Of note, no consensus concerning immunohistochemistry and the detection of immunophenotypical markers existed between the participating centres.

2.3. Clinical assessment

At diagnosis, basic laboratory parameters—sex, age, B-symptoms, performance score (World Health Organization (WHO) grading 0–4), staging (Ann Arbor staging I–IV) including a thorough physical examination with particular attention to all lymphoid regions, bone marrow aspirate and biopsy, chest X-ray or chest computer tomography, and abdominal computer tomography or ultrasonography—were registered in the LYFO.

2.4. Laboratory parameters

Hyperleucocytosis was defined as more than $\geqslant 20\times10^9$/l. Anaemia was defined as a haemoglobin concentration below the reference range (men <8 mM, women <7 mM, respectively). Thrombocytopenia was defined as thrombocyte concentrations below 150×10^9/l. Decreased levels of serum albumin was defined as concentrations below 40 g/l and elevated serum levels of lactate dehydrogenase (LDH) and immunoglobulin (Ig) G was defined as concentrations above 450 U/l and 15 g/l, respectively. Detection of paraproteinaemia and Coomb's test followed standard procedures.

2.5. Therapy

The vast majority of patients ($n=75$) received chemotherapy with CHOP ($n=48$), CNOP, ($n=6$), CEOP ($n=17$), COP ($n=2$), CP ($n=2$) (C, cyclophosphamide; H, hydroxydaunomycin; O, oncovin (vincristine); E, epirubicin; N, mitoxantrone; P, prednisone) or monotherapy with chlorambucil with or without prednisone ($n=25$). 2 patients received the MIME (M, mitoguazon; I, ifosfamide; M, methotrexate (MTX); E, etoposide) and MTX/O/P regimens, respectively. One patient had radiotherapy only. 2 patients received only symptomatic treatment because of a poor clinical condition.

2.6. Assessment of response, disease-free and overall survival

In the LYFO registry, response after primary therapy is registered as complete response (CR) (no detectable disease), partial response (PR) (more than 50% tumour reduction and no detectable new lesions), No Change, Progressive Disease (PD) or as Uncertain or Not Done. Of note, the extent of the response evaluation is not registered in the database and a slight overestimation of

the response rates could not be ruled out. However, evaluation and registering of response were carried out by haematologists and likely followed standard practice with re-examination of previously involved disease sites, including the bone marrow. Disease-free survival (DFS) and overall survival (OS) were calculated from the date of conclusive histology to relapse, PD, death or last follow-up.

2.7. Statistical methods

Statistical analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC, USA) and the observed differences were considered significant if $P < 0.05$. Non parametric comparisons of proportions were performed using the Fisher's Exact test. The Kaplan–Meier method was used in calculation of DFS and OS. No patients were lost to follow-up. Differences in OS and DFS were analysed by the LogRankTest. A Multivariate Cox proportional hazards model was used with forward selection including variables that met the 0.05 significance criteria.

3. Results

3.1. Immunophenotype

Of the 105 cases of MCL included in this study, 74 cases were analysed for pan-B-cell marker (CD19 or CD20) expression and all (100%) were positive. In 57 cases analysed for expression of CD5, 51 cases (89%) were positive and in 38 cases analysed for expression of CD23, 35 cases (92%) were negative. Of the 34 cases of MCL simultaneously analysed for pan-B-cell marker, CD5 and CD23 expression, including the eight cases with atypical cytology, 31 cases (91%) showed an immunophenotype typical for MCL (pan-B-cell marker and CD5 positive, but CD23 negative).

3.2. Incidence rates

During the 8-year period of 1 January 1992 to 31 December 1999, the LYFO study group registered 2790 newly diagnosed NHLs. Of these, 97 (3.5%) fulfilled our inclusion criteria for MCL. 8 cases were diagnosed during the first 6 months of 2000, yielding a total of 105 MCL cases. The mean annual incidence of MCL was 0.42/100 000/year (range 0.38–0.49/100 000/year), 0.7/100 000/year for men and 0.20/100 000/year for women, in the population of 2.88 million inhabitants covered by the registry. Fig. 1, depicting the annual incidence of MCL, shows that although the annual incidence varied for each sex, there was no significant change in incidence during the time period studied for either sex. Fig. 2 displays the age-specific incidence rates. It can be seen that the incidence rate increases with age, and MCL occurs most frequently in the sixth or seventh decade of life.

3.3. Clinical parameters at presentation

Initial clinical features for the MCL population are summarised in Table 1. The median age was 66 years (range 38–89 years) with a male preponderance. Most patients were diagnosed with advanced stage disease.

The dominant site of disease was nodal in the majority of cases, with the neck most frequently affected. Splenomegaly was reported in 37 (36%) of 104 cases of MCL. In the considerable number of cases presenting with predominantly extranodal disease, the bone marrow was the most frequently involved extranodal site followed by the intestines. In 4 cases presenting solely with a single extranodal site, the intestines (2 cases), the femur and the vagina were affected, respectively.

More than a third of the patients presented with anaemia. Albumin was the most frequently affected serum component analysed followed by elevated LDH

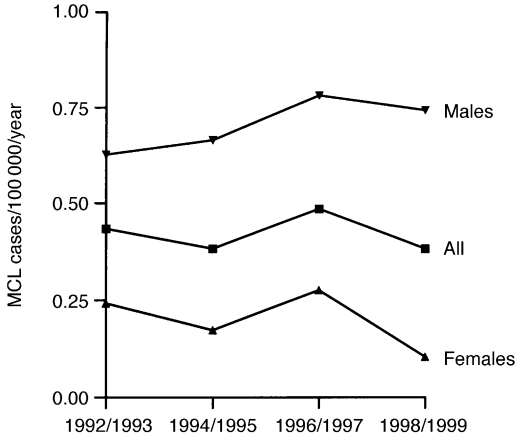

Fig. 1. Annual incidence of all, as well as female and male patients with mantle cell lymphoma (MCL) in western Denmark from 1992 to 1999.

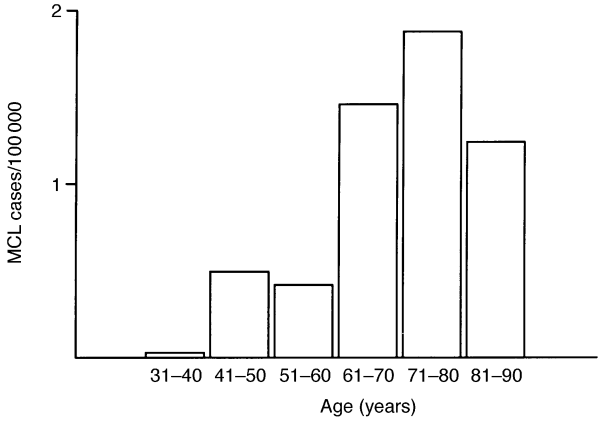

Fig. 2. Age-specific incidences of mantle cell lymphoma (MCL) patients in western Denmark.

and IgG. Of the 9 cases presenting with paraproteinaemia, 3 were IgM and 6 were IgG. Coomb's test was positive in a few cases and not related to presence of paraproteinaemia. Autoimmune disease was not otherwisely examined.

Table 1
Mantle cell lymphoma: clinical characteristics

	n	%
Median age	105	66 years
Sex M/F ratio	79/26	3:1
Performance score (WHO 0–4) $\geqslant 2$	29/105	28
Stage (Ann Arbor)		
I	10/105	10
II	7/105	7
III	4/105	4
IV	84/105	80
B-symptoms	49/100	49
Dominant disease site		
Nodal	70/105	67
Extranodal	21/105	20
Both	14/105	13
Nodal disease sites		
Neck	94/105	90
Aorta (hilus and paraaorta)	73/105	70
Ingven	51/105	49
Axilla	45/105	43
Mediastinum	32/105	30
Pelvis	24/105	23
Tonsils		
Splenomegaly	37/104	36
Extranodal sites		
Bone marrow	75/104	72
Intestines	8/69	12
Liver	6/97	6
Ascites	4/99	4
Salivary glands	4/104	4
Stomach	3/98	3
Bone	2/104	2
Vagina	1/104	1
Testis	1/104	1
Skin	1/104	1
Nasal sinuses	1/104	1
Mamma	0/104	0
Thyroid glands	0/104	0
CNS	0/71	0
Extranodal sites $\geqslant 2$	17/104	16
Only extranodal disease	4/104	4
Anaemia (Hgb: M <8; F <7 (mmol/l))	37/104	36
Thrombocytes <150 (10^9/l)	23/104	22
Leucocytes $\geqslant 20$ (10^9/l)	18/104	17
Elevated serum LDH >450 U/l	40/102	21
Serum albumin <40 g/l	59/100	59
Serum IgG >15 g/l	18/99	18
Serum M-component present	9/91	10
Coomb's test positive	6/84	7

WHO, World Health Organization; CNS, central nervous systeml; M, Male; F, Female; Hgb, haemoglobin; LDH, lactate dehydrogenase; Ig, immunoglobulin.

3.4. Treatment, response and mortality data

There was no consensus concerning the treatment of MCL in the region covered by the registry (see Patients and methods for treatment details). Of note, the age of patients treated with CHOP were significantly younger compared with patients treated with less intensive regimens (CEOP, CNOP, COP, CP, chlorambucil) ($P<0.05$). Of the 97 evaluated cases, 42 (43%) reached CR and 38 (39%) reached a PR. 9 cases only had minor or no change of disease state, and 8 cases had PD after initial therapy. In 8 of the 105 cases, the response was uncertain or not evaluated. Of note, response evaluation followed standard criteria, the exact examined disease sites and the procedure of re-staging in individual cases remains unclarified in the database. Thus, the CR rate is potentially slightly overestimated. In the present series, 78 cases of relapse/PD and 68 deaths were reported after a 9-year observation period. In 44 (65%) of the deceased patients, MCL was the reported cause of death. In 3 cases (4%), death was due to treatment complications. In 2 cases (3%), malignancy other than MCL was reported as the cause of death, and in 10 cases (15%), the cause of death was not related to treatment or malignant disease. The cause of death was unknown in 9 cases (13%). In 53 (91%) of 58 evaluated cases, MCL was present at the time of death.

3.5. Survival

With a mean follow-up of 30 months, the median disease-free survival (DFS) was 15 months (0–105 months), and DFS after 2 years was 32% (SEM 4.9) and after 5 years 18% (SEM 4.5) (Fig. 3a). No plateau was reached in the DFS curve. The median overall survival (OS) was 30 months (1–105 months) (Fig. 3b). OS was 56 (SEM 5.0) and 21% (SEM 5.6) after 2 and 5 years, respectively. As for the DFS rates no plateau was reached in the OS curve.

3.6. Prognostic factors

Table 2 shows the clinical variables with or without influence on the CR rates and survival, as identified by univariate analysis.

CR rates and presence of splenomegaly, bone marrow infiltration, LDH, leucocytosis and B-symptoms were highly significant. Of note, in a sub-analysis of 53 patients, a low proportion of Ki67 antigen-expressing cells (proliferative index $<20\%$) versus a high proliferative index ($>20\%$) had no influence on the CR rates, DFS and OS. This was also the case when the limits specifying low and high proliferative index were set at 10 or 50%, respectively (data not shown).

DFS and OS were correlated to all but one parameter of the IPI: age, performance, stage and LDH con-

centration, but not to the number of extranodal sites. However, the survival curves of the individual risk groups of the IPI as well as the individual stages of the Ann Arbor staging system were not significantly different unless additionally grouped as presented in Table 2. Of note, this was also the case in a sub-analysis of patients treated with CHOP-like regimens only (data not shown). DFS and OS were significantly decreased in patients with MCL disease in the spleen and in patients presenting with anaemia, thrombopenia or leucocytosis. Of note, the presence of bone marrow involvement by itself did not influence survival in this MCL population. The results of the subsequent multivariate analysis of variables of prognostic significance at the univariate level are presented in Table 3.

10 patients with missing variables were excluded from the multivariate analysis. The presence of B-symptoms, leucocytosis and bone marrow infiltration remained of significant influence on the CR rates. In contrast, age, splenomegaly, and anaemia remained significantly adversely correlated to DFS and OS. Of importance, we found no unbalanced age distribution between patients with and without splenomegaly or anaemia ($P=0.12$, $P=0.10$, respectively). In a sub-analysis of MCL patients below 65 years ($n=45$), the OS of cases without splenomegaly and anaemia at the time of diagnosis ($n=29$) was significantly longer, compared with cases with the presence of splenomegaly or anaemia ($n=16$) ($P<0.02$) and, of interest, 58% of the younger patients without splenomegaly and anaemia, equivalent to 38% of all of the younger patients, survive without additional mortality during a prolonged period (Fig. 4). Good performance score affected OS, but was biased by an unbalanced age distribution ($P=0.003$). Of note, in the multivariate analysis, the CHOP regimen significantly increased the CR rates, DFS and OS, compared with other treatments (CEOP, CNOP, COP, CP, chlorambucil) (data not shown). However, as mentioned above, the result was biased by age.

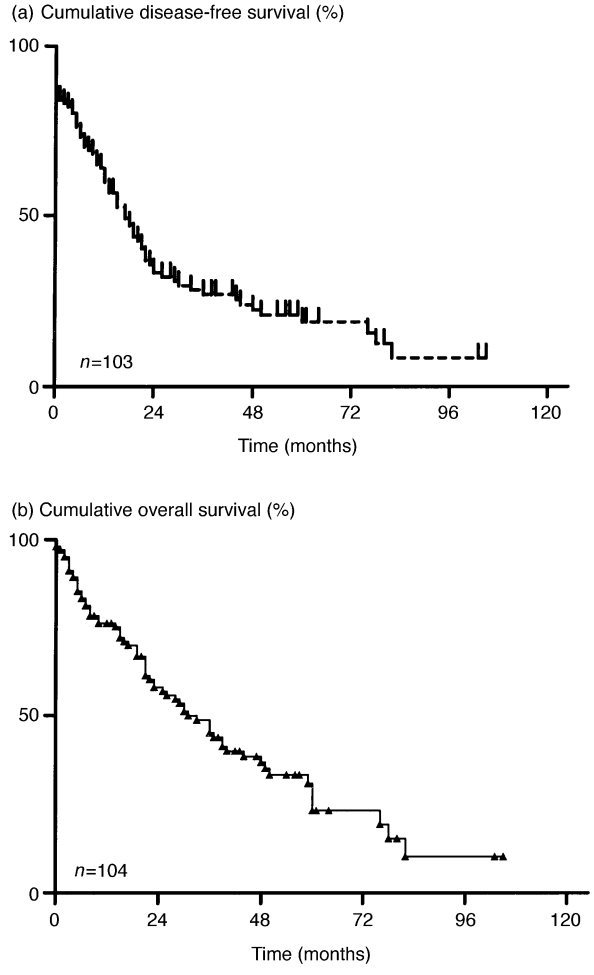

Fig. 3. Estimated disease-free (a) and overall (b) survival for mantle cell lymphoma (MCL) patients in western Denmark. Survival curves are made using the Kaplan–Meier method.

4. Discussion

This analysis of 105 cases of unselected MCL patients, represents the largest series to date, and demonstrate the wide range of presenting clinical features observed in MCL. However, it also confirms the typical MCL patient as an elderly male with a fairly good performance and with an advanced stage disease, often with bone marrow infiltration. It also confirms the high recurrence rate and short survival time, as reported in a previous single institution-based series [13,14].

Although only examined in a smaller subset of patients, a typical MCL immunophenotype was observed in the vast majority of these cases and confirmed the diagnosis of MCL. In line with previous studies, MCL in western Denmark accounts for 3.5% of all NHL cases [6,15]. We found no change of incidence, as has been reported for other NHLs [6,15]. In line with our observation, a recent analysis of NHL incidences in

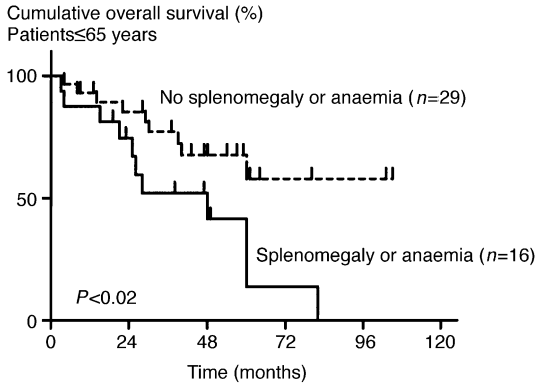

Fig. 4. Estimated overall survival for mantle cell lymphoma (MCL) patients in western Denmark according to absence or presence of splenomegaly and anaemia in patients below 65 years of age. Survival curves were determined using the Kaplan–Meier method. Comparison of survival curves used the LogRank Test.

Table 2
Mantle cell lymphoma: univariate analysis of variables with and without influence on CR rates and survival

		% CR[a]	CR rates Fisher's Exact[a]	n[a]	DFS LogRank[a]	OS LogRank[b]
PS < 2	No	21	**$P = 0.02$**	28	**$P < 0.02$**	**$P = 0.0002$**
	Yes	47		75		
IPI 0-1-2	No	27	**$P < 0.02$**	42	**$P < 0.002$**	**$P < 0.0001$**
	Yes	52		61		
Splenomegaly	No	53	**$P = 0.0005$**	66	**$P = 0.0001$**	**$P = 0.0005$**
	Yes	17		37		
Blood leucocytes	No	42	**$P = 0.002$**	84	**$P = 0.02$**	**$P = 0.02$**
$\geqslant 20$ (10^9/l)	Yes	10		18		
Serum LDH < 450 U/l	No	25	**$P = 0.005$**	40	**$P = 0.01$**	**$P = 0.002$**
	Yes	56		63		
Platelets	No	36	$P = 0.8$	80	**$P < 0.005$**	**$P = 0.0003$**
< 150 (10^9/l)	Yes	30		22		
Hgb. < 8 mM (male)	No	36	$P = 0.15$	66	**$P < 0.0001$**	**$P < 0.0001$**
or < 7 mM (female)	Yes	22		36		
Age > 65 years	No	62	$P = 0.001$	44	**$P = 0.02$**	**$P < 0.006$**
	Yes	29		59		
Stage I + II	No	36	$P = 0.18$	84	**$P < 0.03$**	**$P < 0.02$**
	Yes	56		17		
Dom. site						
Nodal		40	$P = 1.00$	69	**$P < 0.04$**	**$P < 0.03$**
Extra-nodal		37		20		
B-symptoms	No	57	**$P < 0.0001$**	49	$P = 0.051$	$P = 0.09$
	Yes	25		51		
Bone marrow involvement.	No	64	**$P = 0.007$**	27	$P = 0.12$	$P = 0.12$
	Yes	33		75		
Male	No	42	$P = 0.64$	26	$P = 0.77$	$P = 0.79$
	Yes	36		77		
Extranodal sites $\geqslant 2$	No	44	$P = 0.42$	86	$P = 0.26$	$P = 0.30$
	Yes	31		17		
Ki67 < 20	No	43	$P = 0.78$	39	$P = 0.67$	$P = 0.54$
	Yes	50		14		
Serum albumin < 40 g/l	No	32	$P = 0.06$	54	$P = 0.07$	$P = 0.06$
	Yes	53		42		
IgG $\geqslant 15$ g/l	No	45	$P = 0.57$	78	$P = 0.87$	$P = 0.69$
	Yes	33		18		

CR, complete response; DFS, disease-free survival; OS, overall survival; NS, non significant; PS, performance score according to the World Health Organization (WHO); IPI, international prognostic factor index; Dom. site, dominant disease site; Hgb, Haemoglobin; LDH, lactate dehydrogenase; Ki67, proliferative index (% positive cells stained with the Ki67 antibody).

[a] Some of the 105 cases were not evaluable.

[b] P values shown in bold are significant.

Table 3
Mantle cell lymphoma: multivariate analysis of variables with significant influence on CR rates and survival by univariate analysis ($n = 95$)

	CR P value	
B-symptoms	**$P = 0.007$**	
Leucocytes > 20 (10^9/l)	**$P = 0.0006$**	
BM infiltration	**$P < 0.05$**	
	DFS P value	OS P value
Age > 65 years	**$P < 0.003$**	**$P < 0.002$**
Splenomegaly	**$P < 0.0003$**	**$P < 0.002$**
Anaemia	**$P < 0.04$**	**$P = 0.0001$**
Performance score < 2	NS	**$P < 0.02$**

NS, non significant ($P \geqslant 0.05$); BM, bone marrow; CR, complete response; DFS, disease-free survival; OS, overall survival.

1986 through to 1992 showed no increase in MCL cases [16]. However, in accordance with previous studies, we found a 3-fold higher incidence of MCL among men than women [17]. No epidemiological studies have analysed environmental factors associated with the development of MCL and no comparative genomic hybridisation analyses have demonstrated frequent aberrations of the sex chromosomes in MCL, thus, the relationship between MCL and men remains unclarified [18]. Of note, follicular lymphoma, also characterised by a translocation involving the immunoglobulin (*Ig*) gene, does not have a male preponderance [15]. A discrepancy between response and survival in MCL was reflected in our multivariate analysis of prognostic variables. We found the variables important to response completely different to those with an influence on survival. The

survival of MCL patients achieving a clinical CR after therapy is poor and has previously been associated with the presence of minimal residual disease [19]. Moreover, additional cell cycle deregulation, as demonstrated for cell cycle proteins p53 and p27, also plays an important role affecting outcome in MCL [20,21]. It remains to be clarified which factors lead to a decreased survival despite the achievement of a clinical CR after therapy for MCL.

The few long-term survivors with MCL have made the finding of clinical useful prognostic variables difficult. In line with institution-based analyses, we found no significant differences between the survival of unselected MCL patients according to the IPI or Ann Arbor groups unless additionally grouped [6–8,10,22]. Moreover, even after grouping, none of the systems reached significance at the multivariate level. Adding to the lack of significance between the individual groups of both systems is the high frequency of patients presenting with advanced stage disease. Although larger studies are needed to evaluate the significance of the systems, this will not change the fact that only few patients belong to the low risk categories, which will hamper their clinical use. Other prognostic variables have been proposed in previous studies [6–8,10,11,22,23]. However, only a few others have analysed prognostic variables by multivariate analysis. In one large institution-based analysis, LDH, leukaemic MCL and stage were significantly related to outcome [10]. However, as discussed by the authors, the results may have been biased by age and the choice of treatment [10]. The only factors in our multivariate analysis which were adversely correlated to DFS and OS, and not biased by age and treatment, were the presence of splenomegaly and anaemia. Of interest, in a sub-analysis of 45 younger MCL patients without splenomegaly and anaemia, a survival plateau may have formed at almost 60%, but a longer follow-up is needed before final conclusions are reached. As indicated by others, the presence of aggressive MCL subtypes, including cases with a high proliferative index, with frequent spleen infiltration may explain the poor outcome in these cases [11,24]. We did not subclassify MCL cases in histological variants in our study and an association with these and splenomegaly remains to be studied. Of note, blastic variants contribute only a few of all MCL cases and the survival curves of non-blastic variants never reached any sign of a plateau [11]. In contrast to the population-based study from Velders and colleagues, Ki67 expression did not influence survival in our study [6]. However, these differences may reflect technical aspects of the studies [6].

Further development of a more effective treatment in MCL may lead to the finding of clinical variables of improved prognostic value. However, until then splenomegaly and anaemia may prove useful for clinical decisions in younger MCL patients.

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