LYMPHOID NEOPLASIA

Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study

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Key Points

- Rituximab and autologous stem cell transplantation are both independently associated with improved overall survival in mantle cell lymphoma.
- Male gender is an independent negative prognostic factor in mantle cell lymphoma.

There is consensus that young patients with mantle cell lymphoma (MCL) should receive intensive immunochemotherapy regimens, but optimal treatment of elderly patients as well for as patients with limited or indolent disease is not defined. Our aim was to evaluate and compare outcome in relation to prognostic factors and first-line treatment in patients with MCL in a population-based data set. Data were collected from the Swedish and Danish Lymphoma Registries from the period of 2000 to 2011. A total of 1389 patients were diagnosed with MCL. During this period, age-standardized incidence MCL increased, most prominently among males. Furthermore, male gender was associated with inferior overall survival (OS) in multivariate analysis (hazard ratio [HR] = 1.36; *P* = .002). Forty-three (3.6%) patients with stage I-II disease received radiotherapy with curative intent, showing a 3-year OS of 93%. Twenty-nine (2.4%) patients followed a watch-and-wait approach and showed a 3-year OS of 79.8%. Among patients receiving systemic treatment, rituximab (n = 766; HR = 0.66; *P* = .001) and autologous stem cell transplant (n = 273; HR = 0.55; *P* = .004) were independently associated with improved OS in multivariate analysis. Hence, by a population-based approach, we were able to provide novel data on prognostic factors and primary treatment of MCL, applicable to routine clinical practice. (*Blood*. 2014;124(8):1288-1295)

Introduction

Mantle cell lymphoma (MCL) represents 3% to 10% of all lymphomas and is associated with poor prognosis due to aggressive clinical course, low sensitivity to traditionally used chemotherapy, and high relapse rates.[1]

In previous population-based series, the median age at diagnosis was 70 years, with a male/female ratio of 2.3-2.5:1.[2-4] The majority of patients are diagnosed with stage IV disease, and the clinical presentation frequently includes lymphadenopathy and extra-nodal involvement, especially of the bone marrow and gastrointestinal tract.

Although some of the patients do show a highly aggressive course with a survival of <6 months, a minority (~8%) of patients present without symptoms, follow a more indolent course, and may survive more than 10 years even without any treatment.[1] For the small portion of patients with limited stage disease, optimal treatment is still not defined.

Although recent data demonstrate that the median survival of MCL has improved during the last decade,[2] the disease is still regarded as incurable, with a reported median overall survival (OS) of 3 to 4 years. One possible approach to this is the individualization of treatment according to predicted prognosis on standard therapy. Based on data from clinical trials, a specific MCL prognostic index (MIPI) was developed,[5] the prognostic impact of which has also been confirmed in a population-based setting.[6]

However, so far, the choice of treatment in MCL has largely been based on biological age. For young and fit patients, consolidation with total body irradiation and autologous stem cell transplantation (ASCT) was shown to improve survival in comparison with maintenance therapy with interferon-α.[7] The European MCL Network also recently showed that induction with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) alternating with a cytarabine-containing regimen, DHAP (dexamethasone, cytarabine, cisplatin), before ASCT was shown to improve response in comparison with R-CHOP alone as well as improve progression-free survival.[8] A similar regimen is the Nordic MCL2 regimen, which combines rituximab with dose-intensified CHOP and high-dose cytarabine, followed by high-dose chemotherapy and ASCT.[9] This regimen has been shown to be associated with long-term remission and possibly cure in a substantial proportion of patients, most notably among patients with low and intermediate MIPI scores.[10]

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There is an Inside *Blood* Commentary on this article in this issue.

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Because the majority of MCL patients are older and unable to tolerate ASCT, it remains a challenge to find effective treatments for this group. R-CHOP in comparison with CHOP alone was associated with a higher response rate and prolonged time to failure but not OS.[11] In comparison with rituximab, fludarabine, and cyclophosphamide, R-CHOP showed higher response rates as well as superior OS, if combined with rituximab maintenance therapy.[12] In contrast, the German Study Group Indolent Lymphomas have reported results from a randomized phase III trial comparing the combination of R-bendamustine with R-CHOP. Here, R-bendamustine was associated with significantly longer progression-free survival (PFS) in combination with less toxicity.[13]

The aims of this study were to determine the efficacy of different primary chemotherapy regimens in a population-based data set of MCL patients in Sweden and Denmark, including the impact of rituximab and ASCT, in terms of OS to evaluate the therapy options for older patients and to study the incidence over time of MCL as well as the prognosis of MCL in relation to clinical prognostic factors.

Materials and methods

Swedish and Danish lymphoma registries

The study was performed within the Nordic Lymphoma Group framework based on cooperation between the Swedish and Danish Lymphoma Group and their respective population-based registries. The Swedish Cancer Registry, established in 1958, is a dual compulsory report system where all pathological findings of malignancy as well as all patients with newly diagnosed cancer are reported by the responsible pathologist and clinician, respectively. In 2000, the Swedish Lymphoma Group initiated the Swedish Lymphoma Registry, including additional information such as treatment and prognostic factors. The Danish Lymphoma Registry was initiated in 1983 and extended in 1999 to include all patients with lymphoma in Denmark. The study was approved by the regional ethics committee of Lund, Sweden and conducted in accordance with the Declaration of Helsinki.

Study population

The study population includes all patients diagnosed with MCL in Sweden between January 1, 2000 and September 11, 2011 and in Denmark between January 1, 2001 and December 31, 2010. Data were extracted from the national lymphoma registries and in Sweden supplemented by review of patients' records in cases where treatment data were missing. Data on survival status were obtained from the Swedish and the Danish Population Registry.

Statistical analysis

Survival curves were estimated according to the Kaplan Meier method and compared by log-rank tests. Hazard ratios (HRs) for the variables were calculated at both univariate and multivariate levels by Cox regression. For frequency tabulation, the Pearson χ-square and nonparametric tests were used. Values were regarded as statistically significant if $P < .05$. Statistics were performed using SPSS version 20.0. In the analysis of incidence, an additive relative survival model for the computation of P values was used.[14]

Results

Patient characteristics

Patient characteristics are shown in Table 1. A total of 1389 patients (895 from Sweden and 494 from Denmark) were diagnosed with MCL between January 1, 2000 and September 11, 2011. The median age at diagnosis was 71 years with a male/female ratio of 2.5:1. Females showed a significant higher median age at diagnosis (72 years) compared with male patients (70 years) ($P < .01$), and 71% of all patients presented with stage IV disease. Median follow-up time of surviving patients was 107 months. At the time of the analysis, 766 (55%) patients had died.

Table 1. Patient characteristics

	Total		Data on treatment available	Data on treatment not available	*P* value
Number of patients	1389		1197	192	
Median age, years	71 (28-96)		70 (28-95)	72.5 (34-96)	.011
Age, years	N (%)	3-y OS (%)	N	N	
≤65	460 (33.1)	75.7	405	55	.156
>65	929 (66.9)	64.0	792	137	
Gender					
Male	996 (71.7)	55.8	851	145	.206
Female	393 (28.3)	56.7	346	47	
Ann Arbor stage					
I	84 (6.1)	79.5	68	16	.348
II	108 (7.8)	54.7	94	14	
III	167 (12.0)	71.0	149	18	
IV	985 (70.9)	53.4	851	134	
Missing data	45 (3.2)	—	1162	182	
MIPI					
Low risk	172 (12.4)	83.8	152	20	.341
Intermediate risk	323 (23.3)	78.6	297	26	
High risk	604 (43.5)	40.4	554	50	
Missing data	290 (20.9)	—			
LDH					
Normal	769 (55.4)	66.8	665	104	.946
Elevated	564 (40.6)	44.2	487	77	
Missing data	56 (4.0)	—			
WHO performance status					
0-1	1137 (81.9)	64.1	985	152	.375
2-4	238 (17.1)	18.5	201	37	
Missing data	14 (1.0)	—			

Data on first-line therapy was available in 1197 patients (86.2%). The median age in this group was 70 years (range: 28-95), lower than in the group without data on treatment (median age 72.5 years, range: 34-96; $P = .011$). The estimated 3-year survival in the group with data on treatment was 57.8% compared with 45.4% ($P < .001$) in the group without data on treatment.

Age-standardized incidence over time

The incidence of MCL was higher in Denmark during this period, 0.93/100 000 in 2001, increasing to 1.27/100 000 in 2010. Comparative figures for Sweden were 0.57/100 000 in 2001 and 1.09/100 000 in 2010. After adjustment for gender and age, the increased relative risk for MCL in Denmark compared with Sweden was 15.5% (3.2-29.3; $P = .012$). When analyzing the incidence of MCL for males and females separately, a significantly higher relative risk was observed in females in Denmark of 32.7% (7.6-63.7; $P = .008$) compared with Sweden between 2000 and 2010, but no significant difference was observed for males (Figure 1).

The age-standardized incidence changed during the period with an increase of the relative risk of 52.9% (26.2-85.2; $P < .001$). Over time, a significant increase of the relative risk was seen among males in Denmark compared with Sweden, with an increase of the relative risk of 58.9% (26.7-99.4; $P < .001$) during the period. There was no significant change in incidence over time for females (Figure 1).

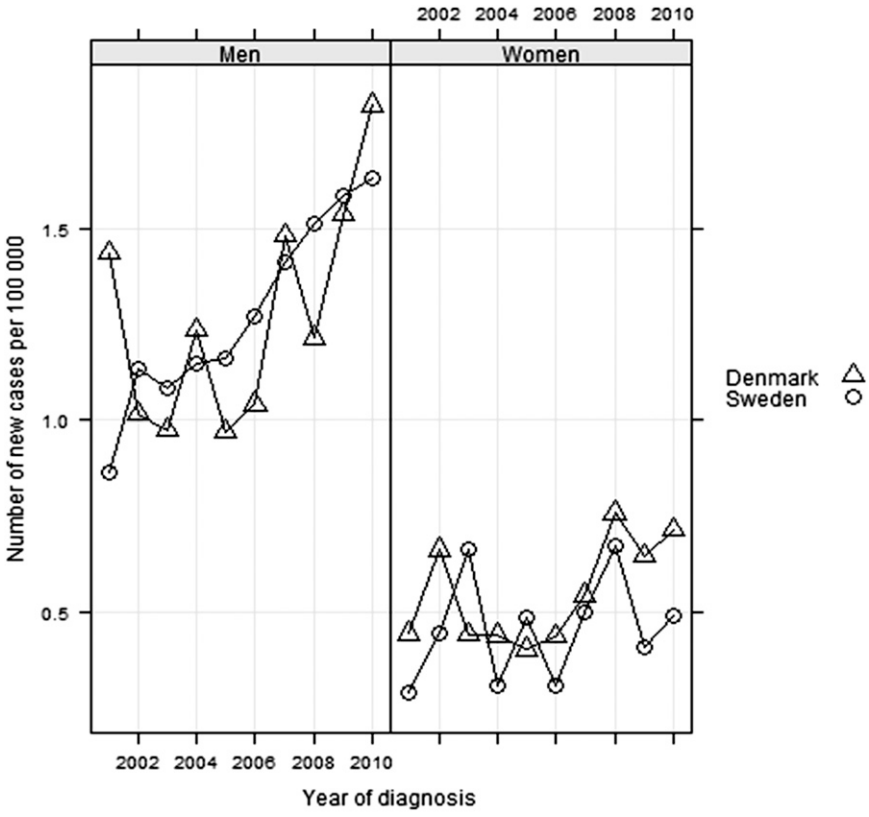

Figure 1. Age-standardized incidence of MCL in Sweden and Denmark.

Survival over time

The estimated 3-year survival for the patients diagnosed from 2000 to 2005 was 51% compared with 61% for patients diagnosed from 2006 to 2011 (Table 1). In univariate analysis, patients diagnosed from 2000 to 2005 were associated with a higher mortality with an HR of 1.3 (95% confidence interval [CI]: 1.1-1.5, $P < .01$) compared with those diagnosed from 2006 to 2011. However, when adjusting for chemotherapy regimen and rituximab, no significant difference in survival was seen between the groups.

Prognostic factors

All parameters included in MIPI (age, performance status, *S*-lactate dehydrogenase (LDH), and white blood cell count) were associated with impaired OS in univariate and multivariate analyses (Table 2). Data on Ki-67 expression were not available. Male sex was not associated with impaired OS in univariate analysis, but when adjusting for age or MIPI, male sex emerged as a negative prognostic factor.

There was no significant difference in survival between patients aged between 40 and 50 and between 50 and 60 years. For patients >60 years, a strong correlation was seen between more advanced age and inferior survival. Twelve patients (<1%) were <40 years at diagnosis. Except for one patient, all of these patients were alive at the time of analysis (supplemental Figure 3, available on the *Blood* Web site).

Treatment modalities

A total of 1066 patients were treated with systemic therapy, and 54 (4.5%) patients received radiotherapy as first-line treatment; 76 (6.3%) patients were given no therapy, of which 29 patients (2.4%) were recorded as active "watch-and-wait." OS for the different groups is shown in Figure 2.

Watch-and-wait

The watch-and-wait group was defined as patients without therapeutic indication for 2 years or more after diagnosis. In the Danish Lymphoma Registry, 16 patients were primarily treated as watch-and-wait, 2 patients in the years 2000 to 2005 and 14 in 2006 to 2012. The Swedish registry did not include specific data on watchful waiting, but after review of medical records, 13 patients were found with active follow-up without any treatment

Table 2. Prognostic factors in MCL

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (per year)	1.06*	1.05-1.07	<.001	1.06*	1.05-1.07	<.001
Male gender	1.04	0.89-1.22	.642	1.36*	1.12-1.64	.002
WHO performance status	1.92*	1.81-2.05	<.001	1.61*	1.47-1.76	<.001
Elevated LDH	1.93*	1.66-2.23	<.001	1.86*	1.55-2.22	<.001
Ann Arbor stage	1.26*	1.17-1.41	<.001	1.21*	1.07-1.35	.002
White blood cell count (per 1×10^9/L)	1.002*	1.001-1.003	.005	1.002*	1.001-1.004	.003

*$P < .01$.

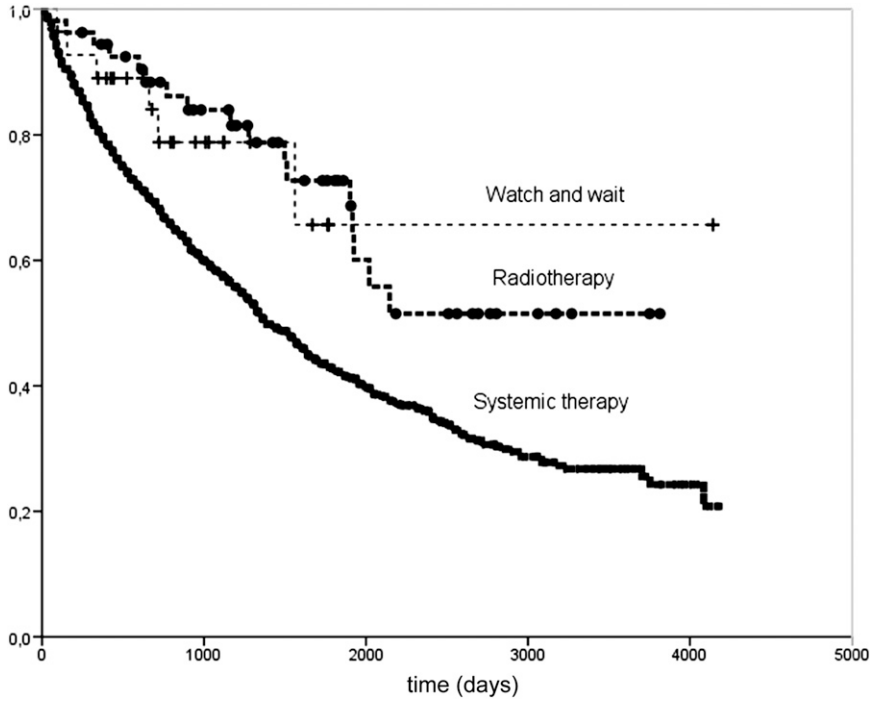

Figure 2. OS according to type of treatment.

from the time of diagnosis until the record review in September 2012 and were classified as watch-and-wait subjects. All of these were diagnosed after 2006. The median follow-up time for these 29 patients was 29 months (3-138) and 3 year-OS was 79%. All patients, of whom 79% were older than 65 years, presented with ECOG Performance status (PS) 0-1 and stage IV disease. Twenty-three patients (79%) presented with normal LDH compared with 57% among the remaining patients ($P = .001$). Median white blood cell count was 11.0, not significantly different from 8.6 for other patients where data were available ($P = .212$).

Forty-seven (3.4%) patients did not receive any treatment due to other reasons such as comorbidities or poor performance status; 89% of these were older than 65 years, 53% presented with stage IV disease, and 58% with a PS of 2 to 4 at diagnosis. The estimated 3-year OS for this group was 21%.

Radiotherapy

Treatment intent was recorded for all patients. Forty-three patients (3.6%), all of whom presented with stage I-II disease, received radiotherapy as primary treatment with a curative intent and showed an estimated 3-year survival of 93%. Eleven patients (0.9%) were treated with radiotherapy as palliative first-line therapy, and the estimated 3-year OS for this group was 56%. Furthermore, 29 patients (2.4%) were given radiotherapy as complementary treatment to primary systemic therapy.

Systemic treatment: distribution and OS

The overall distribution of the most commonly used chemotherapy regimens is shown in Table 3. Of the patients ≤65 years, 375 patients (82%) were treated with systemic therapy, and the estimated 3-year OS for this group was 76% ($P < .001$). The majority of patients (259/404; 64%) received treatment according to the Nordic MCL2 protocol.

Of the 929 patients >65 years, 683 patients (73%) received systemic therapy, and 3-year OS for this group was 46% ($P < .001$). CHOP was the most frequently used regimen, given to 252 patients (37%), followed by chlorambucil, administered in 118 patients (17%). Sixty-five patients (8%) older than 65 years received the Nordic MCL2 (range: 28-83 years), and 20 were ≥ 70 years. In the latter group, the 3-year OS was 65%.

In both age groups, OS was highest for patients treated with the Nordic MCL2 protocol.

Analysis on the distribution of regimens over time showed that CHOP was the most frequently used combination in the first years, followed by Nordic MCL2 and chlorambucil. In later years, Nordic MCL2 emerged as the most commonly used regimen, followed by CHOP and CHOP/Cytarabine (supplemental Figure 2).

Rituximab

Data on rituximab were available for 1151 patients (82%), out of which 766 (67%) patients received this agent. The use of rituximab increased significantly between the period 2000 to 2005 and 2006 to 2011 from 52% to 77% ($P < .001$). The estimated 3-year survival was 57% in the rituximab group compared with 40% in the nonrituximab group ($P < .001$) (Figure 3A).

Rituximab showed a significant association with superior OS in univariate analysis as well as in multivariate analysis when adjusting for gender, MIPI, chemotherapy regimen, and ASCT (HR = 0.66; 95% CI: 0.51-0.85; $P = .001$) (Table 4).

High-dose chemotherapy with ASCT

Data on ASCT were available for 1143 patients (82%), out of which 273 patients (24%) underwent this procedure. The median age of the patients was 58 years (range: 28-70) and almost all (264, 97%) were treated according to the Nordic MCL2 protocol. The estimated 3-year survival was 84% compared with 50% of those who did not undergo ASCT (median age: 73 years). ASCT was associated with a significantly improved OS both in univariate analysis (HR = 0.32; 95% CI: 0.25-0.40; $P < .001$) (Figure 3B) and in multivariate analysis

Table 3. Distribution of different chemotherapy regimens and 3-y OS estimated by Cox regression analysis in MCL

	Nordic MCL2		CHOP		CHOP/cytarabine*		FC		Chlorambucil		Bendamustine		Other regimens†		Cytarabine		CVP	
N	324		310		84		43		132		51		57		30		35	
Median age, years	59		71		70		72		78		72		82		72		77	
3-y OS	79.7%		51.5%		59.5%		53.1%		39.3%		58.7%		28.4%		55.9%		22.9%	
	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS	N (%)	3-y OS
Age, years																		
≤65	259 (79.9)	81.5	58 (18.7)	66.1	13 (15.5)	66.1	6 (14.0)	66.7	14 (10.6)	34.6	4 (7.8)	—	8 (14.3)	62.5	8 (26.7)	72.9	5 (14.3)	60.0
>65	65 (20.1)	72.0	252 (81.3)	48.1	71 (84.5)	57.8	37 (86.0)	50.9	118 (89.4)	39.7	47 (92.2)	62.3	48 (85.7)	24.5	22 (73.3)	50.8	30 (85.7)	16.7
Missing																		
WHO PS																		
0-1	297 (91.7)	82.2	257 (82.9)	58.5	71 (84.5)	65.0	33 (76.7)	66.2	97 (73.5)	47.2	44 (86.3)	59.3	44 (77.2)	39.5	22 (73.3)	66.8	24 (68.6)	25.0
2-4	26 (8.0)	52.6	52 (16.8)	15.5	13 (15.5)	35.9	10 (23.3)	10.0	30 (22.7)	14.7	7 (13.7)	57.1	13 (22.8)	—	8 (26.7)	25.0	11 (31.4)	18.2
Missing	1 (0.3)		1 (0.3)						5 (3.8)									
MIPI																		
Low	93 (28.7)	87.9	19 (6.1)	83.3	8 (9.5)	72.9	1 (2.3)	—	5 (3.8)	53.3	4 (7.8)	—	4 (7.0)	50.0	3 (10.0)	66.7	1 (2.9)	—
Intermediate	91 (28.1)	88.7	96 (30.9)	75.3	24 (28.6)	76.6	11 (25.6)	72.7	20 (15.2)	60.6	13 (25.5)	75.0	4 (7.0)	—	7 (23.3)	83.3	4 (11.4)	25.0
High	93 (28.7)	61.6	145 (46.8)	38.8	36 (42.9)	47.1	25 (58.1)	48.0	83 (62.9)	31.4	29 (56.9)	61.4	41 (71.9)	25.6	17 (56.7)	40.3	27 (77.1)	14.8
Missing	47 (14.5)		50 (16.2)		16 (19.0)		6 (13.9)		24 (18.2)		5 (9.8)		8 (14.0)		3 (10.0)		3 (8.6)	
Rituximab																		
No	0 (0)	—	96 (31.0)	36.7	3 (3.6)	33.3	9 (20.9)	40.0	109 (82.6)	40.0	6 (11.8)	—	27 (47.4)	19.6	5 (16.7)	—	13 (37.1)	23.1
Yes	324 (100)	79.7	195 (62.9)	59.4	81 (96.4)	60.5	34 (79.1)	55.9	19 (14.4)	45.0	45 (88.2)	68.2	24 (42.1)	47.2	24 (80.0)	62.3	19 (54.3)	26.3
Missing			19 (6.1)						4 (3.0)				6 (10.5)		1 (3.3)		3 (8.6)	
Years of diagnosis																		
2000-2005	117 (36.1)	81.2	181 (58.4)	49.1	21 (25.0)	47.6	19 (44.2)	73.7	77 (58.3)	31.2	0 (0)	—	32 (56.1)	25.0	8 (26.7)	50.0	13 (37.1)	23.1
2006-2011	207 (63.9)	78.8	129 (41.6)	55.4	63 (75.0)	66.4	24 55.8)	36.4	55 (41.7)	54.4	51 (100)	58.7	25 (43.9)	41.8	22 (73.3)	51.6	22 (62.9)	22.7

*In this regimen, cytarabine was given at the dose of 1 g/m^2 twice daily, days 1-2 per cycle.

†Other regimens: CVIP (cyclophosphamide, etoposide, idarubicine, prednisone), hyper-CVAD (rituximab + fractioned CHOP alternating with rituximab + high-dose methotrexate/cytarabine), "mini-BEAM" (carmustine, etoposide, cytarabine, melphalan), single rituximab, bortezomib, trofosfamide, vincristine, fludarabine, and cyclophosphamide.

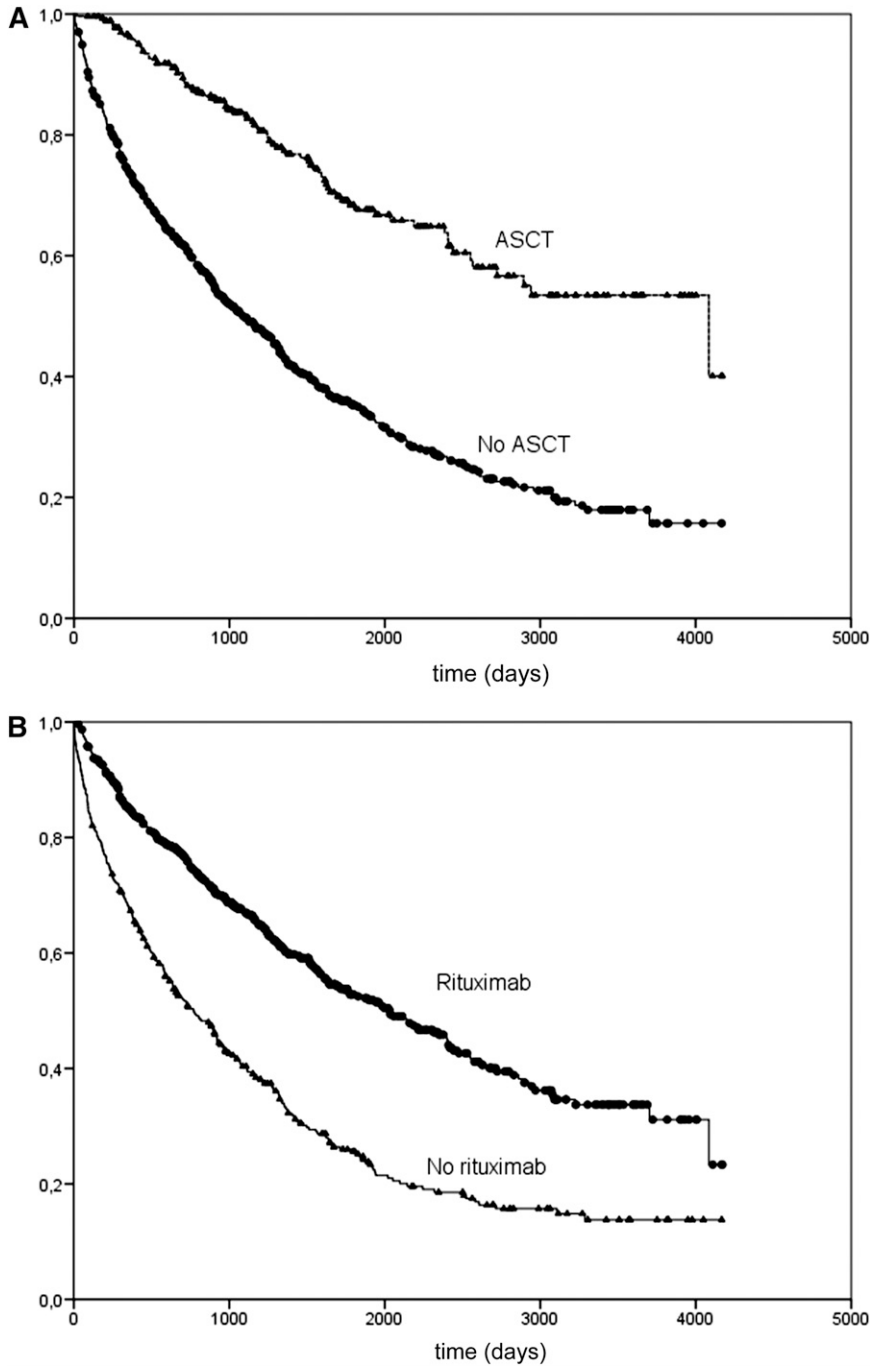

Figure 3. OS of mantle cell lymphoma in a population-based series. (A) OS with or without treatment including rituximab. (B) OS with or without treatment including ASCT.

when adjusting for chemotherapy regimen, rituximab, gender, and MIPI (HR = 0.55; 95% CI: 0.37-0.83; $P = .004$) (Table 4).

Comparison of individual regimens

When comparing the outcome of chemotherapy regimens, all patients with systemic therapy were initially included in the analysis, including adjustment for ASCT, gender, MIPI, and rituximab. Nordic MCL2 and female sex were used as reference categories. Nordic MCL was significantly superior to cyclophosphamide, vincristine, prednisone (CVP), but no other significant differences were seen (Table 4).

In a separate analysis, all regimens that did not involve high-dose chemotherapy were compared with CHOP adjusted for MIPI, gender, and rituximab. Also in this case, only CVP was found to be significantly inferior in terms of survival (HR = 2.23; 95% CI: 1.40-3.56).

CVP was then compared with chlorambucil in a separate analysis, as these regimens are frequently used in patients unable to tolerate CHOP or more intensive regimens. Of all patients, 132 received chlorambucil as first-line therapy and 32 patients were treated with CVP. Rituximab was added to 19 of the patients in each group. When adjusting for MIPI, gender, and rituximab in multivariate analysis, OS was significantly inferior in the group treated with CVP (HR = 2.34; 95% CI: 1.32-4.14; $P = .003$) (supplemental Figure 1). A

Table 4. Multivariate analysis on OS in patients receiving systemic therapy for MCL, adjusted for gender and MIPI

	HR	95% CI	*P* value
Chemotherapy regimen*			
Nordic MCL2	—	—	—
CHOP	1.080	.73-1.59	.698
CHOP/cytarabine	.900	.53-1.52	.692
FC	1.018	.61-1.70	.945
Chlorambucil	1.167	.73-1.85	.514
Bendamustine	1.032	.51-2.10	.930
Other regimens	1.613	.97-2.68	.065
Cytarabine	1.202	.62-2.33	.585
CVP	2.827	1.68-4.76	<.001
Rituximab	.660	.51-.85	.001
ASCT†	.553	.37-.83	.004

*The Nordic MCL2 protocol is used as a reference.
†High-dose chemotherapy with ASCT.

similar multivariate comparison was performed for chlorambucil and bendamustine, adjusted for MIPI, gender, and rituximab. However, chlorambucil was not significantly inferior (HR = 1.12; 95% CI: 0.45-2.8; $P = .80$).

Comparison of individual components

A multivariate analysis was performed to investigate the impact of individual regimen components. Doxorubicin, cytarabine, rituximab, and ASCT were analyzed and adjusted for MIPI and gender. Neither doxorubicin nor cytarabine showed a significant impact on survival, whereas ASCT (HR = 0.59; 95% CI: 0.42-0.82; $P = .002$) and rituximab (HR = 0.68; 95% CI: 0.54-0.85; $P = .001$) were strongly associated with improved survival.

Discussion

Treatment options of MCL have undergone a dramatic development during the last 2 decades. High-dose chemotherapy with autologous stem cell support, high-dose cytarabine, and the introduction of rituximab are important contributors to improved clinical outcome in MCL evolving it into a potentially curable disease, at least for the younger subset of patients. However, relapses do occur, and for elderly or unfit patients, optimal treatment still needs to be defined.

As this is a disease with a relatively low incidence, the use of real-world data is a valuable complement to randomized studies, enabling comparisons of outcome and long-time survival in a large number of patients.

In this series, we found an increased age-adjusted incidence for MCL in males as well as an improved OS for patients diagnosed from 2006 to 2011 compared with those who were diagnosed from 2000 to 2005. Our data confirm previous reports showing an upward trend in the incidence of MCL among men and ethnic whites during 1992 to 2009.[15]

Our results also confirm MIPI as a prognostic tool for MCL. In addition, we show that male gender is an independent negative prognostic factor, also in relation to treatment factors, including regimen, rituximab, and ASCT. In this data set, females were older at diagnosis and received ASCT to a lower extent, which explains why no significant difference was seen in univariate analysis. One possible explanation could be due to pharmacokinetics of rituximab, where a correlation between higher clearance in males and less benefit from rituximab in terms of PFS was observed in patients with diffuse large B-cell lymphoma.[16] However, the difference between males and females remains after adjustments for treatment components including rituximab and consequently needs further explanation.

Age, which is included in the MIPI score, was strongly associated with poor prognosis in patients older than 60 years. Not previously recognized, there is a small population of younger adults, <40 years, with MCL associated with an excellent prognosis, suggesting that this group constitutes a subgroup with distinct/different biological features.

The benefit from rituximab in terms of improved OS in MCL confirms the results of a previous observational study of older patients[17] but has not yet been proved in randomized studies. In this series, we found a significant association between rituximab and prolonged survival in all age groups even when adjusted for MIPI, gender, chemotherapy regimen, and ASCT. Survival in MCL has improved during recent years, and our results strongly indicate that this is related to a more frequent use of rituximab, as this difference is no longer detectable when adjusted for rituximab and chemotherapy regimen.

Among treatment components, ASCT was the factor strongest associated with improved survival independent of age. However, although we have corrected for all prognostic factors available, it cannot be excluded that patients receiving ASCT may have other favorable characteristics, including the lack of comorbidity. We could not show any significant impact on survival of any other individual components of chemotherapy regimens. However, almost all patients (97%) receiving ASCT did so as part of the Nordic MCL2 protocol, including cytarabine, rituximab, and doxorubicin.

Apart from rituximab and ASCT, we were unable to show any significant impact on survival of other components of chemotherapy regimens. This may be explained by the fact that almost all patients receiving ASCT did so as part of the Nordic MCL2 protocol, which includes both doxorubicin and cytarabine in addition to rituximab. Based on the recently presented European MCL data, all younger patients with MCL should receive these agents as part of their induction regimen pre-ASCT,[8] and our results do not contradict this.

Our results indicate that the Nordic MCL2 regimen is an effective treatment of patients with MCL even up to 70 years and that ASCT and rituximab are essential components of this regimen.[9]

For older patients, rituximab was also associated with improved OS and should be considered for all patients receiving systemic therapy. We found no major differences among therapeutic regimens, except that CVP was inferior to CHOP and chlorambucil when adjusted for rituximab and prognostic factors, indicating that this regimen is of limited value in MCL and that chlorambucil may be the preferred chemotherapy for frail patients.

MCL is a very radiosensitive malignancy. In this series, patients with low-stage disease were shown to have a favorable outcome when treated with radiotherapy with curative intent, with 9 of 10 patients surviving after 3 years. A retrospective study on radiotherapy as primary treatment, either in combination with systemic therapy or as single therapy, on stage I-II MCL was recently reported. For patients treated with curative intent, radiotherapy showed high rates of local control (95%) and high survival rates (5-year OS of 62%).[18] Our findings support that radiotherapy may be an effective treatment in localized disease, even when given without systemic therapy. However, we cannot rule out that these favorable results may partly be explained by the low tumor burden in these patients.

The use of the wait-and-watch approach was found to increase during the period of the study and was associated with a favorable 3-year OS of 79%. This increase is probably due to a higher awareness of the existence of indolent MCL.

Today, it is well established that indolent MCL exists as a specific subset with its own clinical and biological features. It is more commonly characterized by a leukemic presentation with no or limited lymphadenopathy, nonelevated LDH, and low proliferation index.[19,20] Our data confirms the important role of identifying these cases accurately to avoid overtreatment.

The strength of a population-based data set is the lack of selection bias, which is present in data from clinical trials. However, in this case, our dataset was not complete in terms of treatment data, especially prior to 2007. The missing cases constitute 14% and were significantly older and characterized by an inferior OS, although similar in terms of MIPI, indicating that there was a bias, likely excluding a population receiving less intensive or no therapy. Another limitation is the lack of pathology review, although the diagnosis of MCL is more reliable and reproducible than for other lymphomas due to the existence of specific markers [cyclin D1 and/or t(11;14)]. Furthermore, the registries do not include data on comorbidity, relapse, second-line therapy, or cause of death.

In summary, by this population-based approach, we are able to compare outcome and long-time OS on an unselected group of patients that would never be subjected to randomized trials. We could confirm that that radiotherapy is a valid option for localized MCL as well as the use of a watch-and-wait approach for nonsymptomatic MCL. In addition, we establish that both rituximab and ASCT are essential components of systemic therapy regimens in MCL associated with improved OS.

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Authorship

Contribution: M.J., P.N.B., and C.H.G. designed the study; A.A., S.B.-W., P.N.B., L.M.P., F.D., H.N.-E., P.J., M.P., and M.J. collected data; and A.A., A.A.-L., and M.J. analyzed the data and wrote the paper.

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