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Marked improvement of overall survival in mantle cell lymphoma; a population based study from the Swedish Lymphoma Registry

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Running title

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Abstract

In recent years, more intensive chemotherapy regimens for mantle cell lymphoma (MCL) have been associated with prolongation of survival. In this study, our aim was to investigate prognostic factors and evaluate improvement in survival in MCL on a population level. The cohort included all patients diagnosed with MCL from 2000-01-01 to 2010-03-31 in the Swedish Lymphoma Registry.
785 patients with MCL were identified. Age, performance status and B-symptoms were significant prognostic factors for overall survival (OS) in multivariate analysis. In addition, OS was markedly improved (HR=0.8, 95% C.I. 0.7-0.9) for patients diagnosed during the latest time period, 2006-2010, also when corrected for prognostic factors as above. Estimated OS at 3 years was 62%, compared to 47% for patients diagnosed earlier ($p<0.01$). The reasons for this dramatic improvement in OS are not yet clear, but may be due to the introduction of specific and more potent therapeutic regimens.

Introduction

Mantle cell lymphoma (MCL) is a distinct type of lymphoid neoplasm characterized by the t(11;14) translocation, by which the cyclin D1 gene on chromosome 11 is translocated to the enhancer of the IgH gene on chromosome 14. This translocation leads to an overexpression of cyclin D1 protein which is important for G1-S transition and cell cycle progression. By the time of its characterization in the early 1990´s, MCL was considered among the most aggressive and chemotherapy-resistant lymphoma subtypes[1].
MCL accounts for approximately 3 to 10% of all cases of lymphoma with a predominance of the male sex (~2:1 or greater) with a median age of 70 years.

Genetically, MCL is more homogeneous than most other B-cell lymphomas, but the clinical course may be very variable. Possibly, patients with different clinical profile may benefit from specific therapeutic strategies. Recently, a specific MCL prognostic index (MIPI) was introduced, based on four independent prognostic factors which are easily and routinely available in clinical practice: age, ECOG/WHO performance status, lactate dehydrogenase level (S-LDH) and leukocyte count. MIPI is able to clearly separate patients into three risk groups with distinct overall survival (OS). The prognostic impact of the MIPI was recently evaluated in a population-based dataset from the Netherlands, where the authors proposed a modification by the addition of gender and B-symptoms, thus improving the discrimination of the three groups[2]. The strongest biological predictor of prognosis in MCL is proliferation, measured by number of mitoses, Ki-67-expression or a proliferation signature by gene expression profiling[3].

In recent years, a number of therapeutic options have been developed specifically for MCL. Initially, the standard treatment for MCL was CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) [7]. The addition of rituximab to CHOP is associated with a significantly higher response rate and a prolongation of time to treatment failure (TTF), but with median TTF of less than 3 years [4].
Consolidation with autologous stem cell transplantation (ASCT) has been shown to prolong progression-free survival compared to interferon maintenance, and is now routinely used in younger patients[5]. To improve induction therapy before ASCT, high-dose cytarabine and rituximab was added in the Nordic Lymphoma Group (NLG) MCL2 trial. In this trial, a substantial proportion, 2/3, achieved long term remission [6]. The improvement in outcome by addition of cytarabine was recently confirmed in a randomized trial by the European MCL Network[7].
There is less consensus about standard treatment for elderly patients, and until recently the most commonly used therapy has been R-CHOP. However, preliminary data from the German StIL Group indicate that the combination of rituximab and bendamustine (R-B) is considerably less toxic and more efficacious than R-CHOP[8].
Our aim in this study was to examine prognostic factors for overall survival of MCL in a population-based dataset, and to evaluate possible improvement in outcome during the past decade.

Materials and methods

Swedish Lymphoma Registry

The Swedish Cancer Registry, developed in 1958, is a nation-wide compulsory dual report system where all pathology specimens indicating malignancy are reported by the pathologist to the Regional Oncology Center, and all patients with a newly diagnosed cancer are reported by the clinic responsible. Since all the lymphoma subtypes are grouped together in the Swedish Cancer Registry, a more specific registry for lymphoma was required. The national Swedish Lymphoma Group (SLG) was founded in 1979 to facilitate research and optimize treatment for patients with malignant lymphoma in Sweden. The SLG initiated the Swedish Lymphoma Registry in 2000. When a patient with lymphoma is included in the Cancer Registry, the Regional Oncology Center sends a form requesting additional information to the attending clinician. In this way data such as diagnosis, dissemination of the disease, prognostic factors and patient characteristics are collected by the Regional Oncology Centers in each of the six Swedish health care regions, and thereafter unidentified and transferred to a national database. SLG is, in collaboration with Regional Oncology Centers, responsible for the Swedish Lymphoma Registry and national reports are presented yearly. Since 2007, the registry is web-based, which facilitates the input and application of data. In order to enhance the immediate clinical value of the registry, a form including details on first-line treatment has been introduced, since January 1, 2007.

Study population

The study population included all patients with MCL included in the Swedish Lymphoma Registry from January 1, 2000, to December 31, 2009. According to the national pathology guidelines, expression of cyclin D1, or the demonstration of t(11;14) was required for the diagnosis of MCL.Data collected were age, gender, Ann Arbor stage, B-symptoms, type extra nodal presentations, number of extranodal sites, bulky disease, S-LDH level, WHO performance status, IPI, and year of diagnosis. Data on survival status and overall survival were obtained from the Swedish Population Registry.

Statistical methods

Survival curves were estimated according to the Kaplan Meier method and compared by log-rank tests. Univariate survival analyses by Cox regression were performed and for factors that showed statistical significance ($p<0.05$), a multivariate analysis of overall survival was performed. For interrelationships among prognostic factors, chi-square tests were used. For analysis of differences in composition between groups, Mann-Whitney test was used. Statistical analyses were performed using SPSS 17.0.

Results

Patient characteristics

In total, 785 patients with MCL were identified in the Swedish Lymphoma Registry during the period of 2000 to 2010. The yearly incidence of MCL was 0.85 per 100 000, comparable to previous findings[9]. The patient- and disease specific characteristics of these patients are presented in Table I. The median age was 71 years, with a clear male predominance. The majority of patients presented with Ann Arbor stage IV and extra

nodal involvement. In total, 451 patients (57%) died during this observation period. Among surviving patients, the median time of follow-up was 41 months.

Age

The median age of the study population was 71 years, ranging between 35 and 93 years. As expected, there was a strong relation between age and overall survival (Table II, Figure 1), with the largest gap among the survival curves between patients over and under the age of 60. The estimated 3-year survival for patients 60 years or younger was 81%, compared to 44% in patients older than 60. The hazard ratio (HR) for overall survival between these groups was 3.8 (95 % C. I. 2.8-5.2) in the univariate analysis and 3.4 (2.4-4.7) in the multivariate analysis.

Gender

As expected, the majority of patients were male (72 %). Although the median age of women were slightly higher, 73 vs. 70 years (p=000.3), there was no significant difference in overall survival, even after correction for age.

Performance status (WHO)

Data on WHO Performance status (PS) at the time of diagnosis were available in 770 patients (98%), of whom the majority (80%) presented with PS 0-1. PS was also a strong predictor of overall survival, both in the univariate and multivariate analysis (Table II).

S-LDH

Data on serum lactase dehydrogenase (S-LDH) level at diagnosis were available in 737 patients (94 %) and 319 of these patients (43%) presented with elevated S-LDH. S-LDH proved statistically significant as a prognostic factor for overall survival in the univariate analysis (HR=1.8, 95 % C. I. 1.5-2.2) but not in the multivariate analysis (Table II).

Ann Arbor stage

Data on stage were available in 764 patients (97 %) out of which a majority (70 %) presented with stage IV at the time of diagnosis. Estimated 3-year survival for patients with stage I-III was 63%, compared to 48% for stage IV. The HR for overall survival between these patient groups was 1.7 in the univariate analysis (95% C. I. 1-3-2.1), but not statistically significant in the multivariate analysis (Table II).

Extranodal presentations

The three most frequent extranodal presentations were bone marrow (60 %), large bowel (7 %) and gastric involvement (4 %). Bone marrow involvement was associated with adverse overall survival in the univariate analysis (HR = 1.4, 95% C. I. 1.2-1.7), but not in the multivariate analysis (Table II). There were 7 patients with CNS involvement at diagnosis. None of these patients survived, with a median survival of 16 months. Other presentations, or the number of extranodal sites, were not associated with overall survival.

B-symptoms

The presence of B-symptoms at diagnosis was noted in 42% of the patients in this series. This was associated with inferior overall survival in univariate as well as multivariate analysis (Table 2). The most frequent B symptom was weight loss (30%), followed by nightly sweats (22 %). All three B-symptoms were associated with adverse overall survival in univariate analysis, but were not included in the multivariate model (Table II).

Interrelationships among prognostic factors

Elevated levels of S-LDH were more frequent among patients with PS 2 or more, where 70 % had elevated levels, compared to only 38 % in patients with PS 0-1 ($p < .0001$). LDH was also more frequently elevated among patients with stage IV, 49% compared to 27% among patients with stage I-III ($p<0.0001$), and among patients with B-symptoms ($p<0.0001$). Patients with stage IV more frequently presented with poor PS ($p=0.02$) and B-symptoms ($p<0.0001$).

As expected, we found more patients with high PS in the older age group (>60 years) ($p<0.01$), and among patients with B-symptoms ($p<0.0001$). No relation between PS and age, and no evidence for a relationship between age and S-LDH, stage or B-symptoms was noted.

Period of diagnosis

To investigate whether an alteration in overall survival during this time frame could be detected, we split the patient group in two, those diagnosed before December 31, 2005, and those diagnosed later. The median time of follow-up among patients alive was 76 and 26 months respectively. No significant difference in prognostic variables between the groups could be seen (Table II). We found a marked improvement in overall survival between these patient cohorts (HR=0.8, 95% C. I.: 0.7-0.9). This difference persisted also in the multivariate analysis (Table II). Estimated three-year survival was 47% for patients diagnosed 2000-2005, and 62% for patients diagnosed 2006 or later (Figure 2). The improvement was even more prominent among patients with favorable PS (0-1), HR=0.6, 95% C. I.: 0.4-0.8. In patients with poor PS or in patients <60 years, no improvement in survival could be demonstrated.

Treatment

Detailed data on primary treatment was available for patients diagnosed from January 1, 2007, comprising 133 patients. Nine patients (7 %) received primary radiotherapy only, and 124 patients were treated with chemotherapy. In the majority of patients (107/124, 86 %), the treatment included rituximab. Five patients received radiotherapy in addition to chemotherapy.

The most frequently used regimen was the Nordic Lymphoma Group MCL2 protocol (NLG-MCL), including escalated CHOP, high dose cytarabine, rituximab and high dose chemotherapy with autologous stem cell support. This regimen was used in 34 of 124 patients (27%), mostly in younger patients (median age 58 years, range 40-70). Nineteen of these were treated within a clinical trial. Standard R-CHOP was used in 26 patients (21%), and 24 patients (19%) received alternating R-CHOP and R-cytarabine without high-dose chemotherapy. R-bendamustine (RB) was used in ten patients (8 %), and the remaining received a number of diverse regimens (Table III).

Two regimens were associated with favourable survival in this dataset. For patients treated with the NLG-MCL regimen, 33 of 34 patients are alive after a median of 23 months of follow-up. The outcome was not different for patients treated outside the clinical trial, all 15 patients are alive after a median of 25 months of follow-up. For patients receiving RB, 9 of 10 patients are alive after a median of 18 months of follow-up.

Discussion

The development of therapeutic options for patients with mantle cell lymphoma has been quite dramatic during the last two decades. MCL is characterized by a lower sensitivity to anthracyclins, compared to other B-cell lymphomas, but this may be counter-balanced by addition of other agents, such as cytarabine, bendamustine and rituximab.

For younger patients, the most potent regimens include high dose cytarabine, rituximab, and high dose chemotherapy with stem cell support, exemplified by the R-hyper-CVAD, the Nordic Lymphoma Group MCL2 protocol, and the European MCL Network R-CHOP/DHAP regimen. For older patients, there is less available evidence concerning optimal treatment. Following the presentation from the German STiL Group, showing superior outcome associated with less toxicity with the R-bendamustine regimen in patients with MCL >60 years, compared to R-CHOP, the use of the former combination has been frequently used.

In this population based series of MCL, we found age, performance status (PS) and the presence of B-symptoms to be associated with overall survival in univariate and multivariate analysis. As the majority of patients with MCL present with Ann Arbor stage IV, and more than one extranodal site, it was not surprising that these factors was not prognostic in this series. A surprisingly low fraction of the patients were registered with having gastrointestinal involvement. This is probably due to the lack of uniform staging criteria in this population based series, and is likely to be under-reported. Although the majority (68%) were classified as stage IV, this figure may have been higher if endoscopic evaluation had been performed in all patients.

LDH was found to be a prognostic factor in univariate analysis, but not in the multivariate model, due to an association with poor PS and the presence of B-symptoms.

Recently, a specific prognostic index for MCL has been proposed, the MIPI, based on data from 455 patients included in trials by the European MCL Network. This index includes the following four factors: age, PS, LDH, and leukocyte count (WBC). In addition, cell proliferation as assessed by Ki-67-expression, showed strong additional prognostic relevance. Comparing these two datasets, we found a similar HR for age and PS in univariate and multivariate analysis, although the median age of the MIPI dataset was ten years lower, 60 years. Likewise, stage and extranodal sites were not independent prognostic factors in both studies. Unfortunately, we had not access to WBC in this series, and were thus unable to confirm the prognostic impact of this index in our population. Compared to the population based study by van de Schans et al, we were unable to confirm the prognostic impact of gender, but we found a similar HR for B-symptoms and PS [2].

A positive finding of the study was that overall survival has improved considerably in this population during the last decade. One possible reason may be that more cases of the more indolent leukemic form are diagnosed as MCL, due to more frequent use of immunophenotyping and immunohistochemistry for cyclin D1. On the other hand, there

was no notable increase in the incidence of MCL during this time period. Improvement in supportive care, such as use of G-CSF and the treatment of neutropenic infections may also explain part of the superior survival in the later time period.
Another possible reason is, the introduction of MCL specific regimens, such as the NLG-MCL2 for younger patients. We only had access to detailed treatment data for a minority of the patients (17%), registered from 2007 and later. From this limited data, with short time of follow-up, we are unable to draw firm conclusions and as the patient groups are not comparable in terms of prognostic factors, these results should be interpreted with caution. Still, the results with the NLG-MCL2 regimen are encouraging, with 33 out of 34 patients alive after a median of 2 years of follow-up. Also with R-bendamustine, the highly preliminary results are better than expected.

There are only a few published population based series of MCL, of which this is the largest. Compared to data from clinical trials, an evident limitation of our study is that the data have not undergone monitoring. In addition, as the data were based on anonymized data reported by clinicians nationwide, we were not able to access individual patient's records to perform a pathological review. Nor were we able to obtain data on biological prognostic parameters, such as Ki67 expression. On the other hand, our series may more accurately reflect the complete picture of MCL in the general population, as selection bias is minimized.

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Table I

Characteristics of the 785 patients diagnosed with MCL in the Swedish Lymphoma Registry, in total and according to period of diagnosis

Variable	2000-2005	2006-2010	Total
Median age, years (range)	71 (35-95)	71 (36-93)	**71 (35-95)**
	No. (%)	No. (%)	**No. (%)**
Male sex	337 (69.9)	226 (74.6)	**563 (71.7)**
Ann Arbor Stage			
Stage I	35 (7.3)	15 (5.0)	**50 (6.4)**
Stage II	50 (10.4)	24 (7.9)	**74 (9.4)**
Stage III	59 (12.2)	43 (14.2)	**102 (13.0)**
Stage IV	326 (67.6)	212 (70.0)	**538 (68.5)**
Missing Data	12 (2.5)	9 (3.0)	**21 (2.7)**
International Prognostic Index (IPI)			
Low Risk	90 (18.7)	46 (15.2)	**136 (17.3)**
Low Intermediate Risk	142 (29.5)	110 (36.3)	**252 (32.1)**
High Intermediate Risk	132 (27.4)	83 (27.4)	**215 (27.4)**
High Risk	69 (14.3)	37 (12.2)	**106 (13.5)**
Missing data	49 (10.2)	27 (8.9)	**76 (9.7)**
Extranodal sites			
0	125 (25.9)	86 (28.4)	**211 (26.9)**
1	267 (55.4)	162 (53.5)	**429 (54.6)**
2	68 (14.1)	43 (14.2)	**111 (14.1)**
3	16 (3.3)	9 (3.0)	**25 (3.2)**
4	3 (0.6)	2 (0.7)	**5 (0.6)**
5	3 (0.6)	1 (0.3)	**4 (0.5)**
Gastric involvement	19 (3.9)	12 (4.0)	**31 (3.9)**
Large bowel involvement	32 (6.6)	21 (6.9)	**53 (6.8)**
Bone marrow involvement	294 (61.0)	178 (58.7)	**472 (60.1)**
Bulky disease (>10 cm)	59 (12.2)	28 (9.2)	**87 (11.1)**
Missing data	24 (5.0)	13 (4.3)	**37 (4.7)**
Elevated LDH	202 (41.9)	117 (38.6)	**319 (40.6)**
Missing Data	33 (6.8)	15 (5.0)	**48 (6.1)**
B symptoms	207 (42.9)	121 (39.9)	**328 (41.8)**
Missing data	19 (3.9)	12 (4.0)	**31 (3.9)**
Performance status (WHO)			
0-1	386 (80.1)	241 (79.5)	**627 (79.9)**
2-4	88 (18.3)	55 (18.2)	**143 (18.2)**
Missing data	8 (1.7)	7 (2.3)	**15 (1.9)**
Total number	482	303	**785**

Table II

Prognostic factors for overall survival according to univariate and multivariate Cox regression analyses

Prognostic factors			*Univariate*		*Multivariate*	
		Estimated 3-year survival	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**
Age	≤60 >60	81% 44%	3.8***	2.8-5.2	3.4***	2.4-4.7
Sex	Female Male	52% 51%	1.1	0.9-1.3	–	
Performance status (WHO)	0-1 ≥2	60% 14%	4.4***	3.5-5.4	3.2***	2.4-4.1
Ann Arbor Stage	I-III IV	63% 48%	1.7***	1.3-2.1	1.3	0.9-1.9
Serum LDH	≤1xNUL >1xNUL	61% 41%	1.8***	1.5-2.2	1.2	0.9-1.4
Extranodal sites	0-1 ≥2	52% 46%	1.1	0.9-1.5	-	
Bone marrow involvement	No Yes	56% 48%	1.4**	1.2-1.7	1.0	0.7-1.4
Gastric involvement	No Yes	52% 41%	1.1	0.7-1.8	-	
Large bowel involvement	No Yes	51% 54%	0.9	0.6-1.3	-	
B-symptoms	No Yes	63% 31%	2.0***	1.6-2.4	1.5**	1.1-1.8
Weight loss	No Yes	57% 36%	1.9***	1.5-2.3	1.0	0.7-2.0
Nightly sweats	No Yes	53% 38%	1.5**	1.2-1.8	-	
Fever	No Yes	52% 31%	1.8***	1.3-2.4	-	
Bulky disease	No Yes	54% 40%	1.4*	1.1-1.9	0.9	0.7-1.2
Period of diagnosis	2000-2005 2006-2010	47% 62%	0.8**	0.7-0.9	0.8**	0.7-0.9

*: p<0.05, **: p<0.01, ***p<0.001

CI: Confidence interval LDH: Lactate dehydrogenase NUL: Normal upper limit

Table III

Chemotherapy regimens for MCL for 124 patients in the Swedish Lymphoma Registry 2007-2010

Regimen	Number of patients	Median age, years (range)	Number of cycles (range)	Estimated 2-year survival
R-Bendamustine	10	73 (59-81)	**4 (1-6)**	**90%**
R-CHOP	26	76 (64-83)	**5 (1-8)**	**61%**
Chlorambucil +/- rituximab	9	85 (77-93)	**2 (1-6)**	**33%**
R-CHOP+Cytarabine	24	68 (47-80)	**6 (1-6)**	**64%**
R-MAXI CHOP+Cytarabine + HDSCT (Nordic Lymphoma Group MCL2/MCL3)	34	58 (40-70)	**Not applicable**	**97%**
Other*	21	81 (52-90)	**6 (1-8)**	**31%**
Total	124	71 (40-93)	**6 (1-8)**	**68%**

*CHOP=5, R-FC=4, R-COP=2, R-Cytarabine=2, Trofosfamide=2, Cyclophosphamide=2, CVIP=2, DA=1, Chlorambucil+Etoposide=1.

<50 years

50-60 years

60-70 years

70-80 years

>80 years