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Improvement in survival of diffuse large B-cell lymphoma in relation to age, gender, IPI and extranodal presentation: a population based Swedish Lymphoma Registry study

Running title: Population based study of DLBCL

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Abstract

Our aim was to describe a large population-based cohort of diffuse large B-cell lymphoma (DLBCL) during the last decade, evaluating possible improvement in survival and to identify subgroups in need of novel treatment strategies. The study population encompassed all patients diagnosed with DLBCL in Sweden from 2000 through 2010.
5349 patients were identified. There was no increase in incidence for females, but for males, there was an estimated yearly increase in incidence by 0.019 per 10 000. When adjusted for age and gender, the improvement in overall survival for the whole group was estimated at 4.5% per year, most prominent in the age group 60-78 years, and in patients with good performance status. In this large dataset, we were able to detect a clear improvement in overall survival in DLBCL, although restricted to specific prognostic subgroups, and to identify specific disease presentations that significantly affect overall survival.

INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of lymphoma. In Sweden the incidence is approximately 5.5 patients per 100 000, corresponding to 25% of all malignant lymphomas. Since the introduction of modern chemotherapy (dose-dense regimens and the addition of immunotherapy), approximately 50% of patients with DLBCL are cured [1-4]. The prognosis is strongly dependent on clinical factors, as summarized in the IPI (International Prognostic Index). Within clinical trials, the outcome of patients with DLBCL has shown a gradual improvement, but less is known about the impact in the population at large, or what subgroups of patients that most have benefited from the improvement in therapy. The Swedish Lymphoma Registry (SLR) started in 2000, and has almost full coverage of patients with malignant lymphoma in Sweden. This study describes a population-based cohort of DLBCL patients, evaluating the possible improvement in survival during the period 2000-2010, in relation to patient age, prognostic groups and disease presentation. Our aim was to identify specific subgroups in need of novel treatment strategies.

MATERIALS AND METHODS

The Swedish Lymphoma Registry

This is a retrospective study based on the population-based Swedish Lymphoma Registry. As previously reported, this registry was established in 2000 by the national Swedish Lymphoma Group (SLG) to provide a more detailed registration of patients with malignant lymphomas[5]. Compared to the compulsory Swedish Cancer Registry, the Swedish Lymphoma Registry displays coverage of approximately 95-97% of all lymphoma cases in Sweden. In total, 49 hospitals treat lymphoma patients and report to the SLR.

Study Population

The study population included all patients diagnosed with DLBCL in Sweden from January 1, 2000 to December 31, 2010, and included in the Swedish Lymphoma Registry. Patients with primary CNS lymphoma or HIV-related lymphoma were excluded. Data collected were year of diagnosis, gender, age, Ann Arbor stage, serum-LDH level, WHO performance status, number of extranodal sites, type of extranodal involvement, B-symptoms and the presence of bulky disease (maximum diameter >10 cm), and if treatment with curative intent was delivered. Data on survival status were obtained from the Swedish Population Registry, and updated as of May 14, 2013.

Statistical Methods

Survival curves were estimated according to the Kaplan-Meier method and compared by log-rank tests. The Cox regression model was used for uni- and multivariate analysis. For evaluation of the prognostic impact of clinical risk factors and disease presentations, a Cox model with one term for the sex dependence and two terms, one linear and one quadratic, accounting for the age dependence was used. The assumption of proportional hazards was checked graphically. For the dependence of year of diagnosis, the assumption of proportional hazards could not be validated. Therefore, stratification by year of diagnosis (one-year classes) was used. For interrelationships among prognostic factors, chi-square tests were used. Chi-square test and linear by linear association was used for comparisons of the time periods. Age-standardized incidence was calculated according to the direct method (general population Sweden 2000). Linear regression was used for estimation of differences in age-standardized incidence. Breslow estimates were used for the survival curves in Figures 1 and 2. Statistical analyses were performed using SPSS v 18 and R version 2.12.0.

RESULTS

Patient Characteristics

In total, 5349 patients diagnosed with DLBCL were identified in the Swedish Lymphoma Registry

during 2000-2010. The median follow-up-time of surviving patients was 80 months. Patients' characteristics are summarized in Table I.

Age and Gender

The median age for all patients was 70 years (range 16-99, quartiles 60-79). A majority were males, 2919 cases (55%). The median age for males was lower, 69 years (range 17-96, quartiles 59-77) compared to females, 72 years (range 16-99, quartiles 61-80) ($p<0.001$). The relative risk for overall survival in univariate analysis between these groups was not statistically significant (1.02 C.I. 0.95-1.10, $p=0.62$). However, if stratified for age, stage, S-LDH, extranodal sites and performance status, the risk for men was higher: RR= 1.17 (95% C.I.:1.06-1.28) ($p=0.001$). This difference was constant during the observation period.

As expected, a pronounced association between age at diagnosis and overall survival was noted. Dividing the population was into quartiles, the estimated 5-year survival for the youngest quartile was 74% compared to 22% for patients in the oldest quartile (≥79 years) (Figure 1).

Age-Standardized Incidence

During the whole period, the incidence was higher for men. There was no increase noted for females, with a constant age-standardized incidence of 0.65/10 000. For males, however, there was an estimated yearly increase in incidence by 0.019 per 10 000, from 0.68 in 2000 to 0.90 in 2008 ($p=0.005$) (Figure 1).

Prognostic Factors

As expected, in addition to age, all factors included in the International Prognostic Index (IPI), i e stage, WHO performance status (PS), number of extranodal sites and S-LDH, were strongly related to survival. IPI were possible to calculate in 4929 patients (92 %), with most patients distributed in the groups with IPI 1 to 4. The distribution of IPI groups did not change during the time period. The presence of B-symptoms was also associated with adverse overall survival, after adjustment for age, gender and year of diagnosis; the relative risk was 1.64 (95% C. I.: 1.52 – 1.77, $p<0.0001$). In addition, bulky disease (maximum diameter >10 cm) was associated with

significantly higher relative risk, 1.40 (95% C. I.: 1.28-1.53, p<0.0001), after adjustment as above. When the prognostic impact of B-symptoms and bulky disease were evaluated in a Cox model together with IPI, their presence did not provide additional independent prognostic information.

Extranodal Presentations

The most frequent extranodal presentation was bone marrow involvement, present in 634 (12%) cases followed by skeletal in 407 (8%), gastric in 335 (6%), lung 259 (5%), and liver 242 (4%) cases. The frequencies of extranodal presentations were consistent across the regions in Sweden. When adjusted for age, gender, stage, S-LDH, performance status and number of extranodal sites, the RR for poor overall survival was highest for patients with CNS involvement, RR= 2.18 (95% C. I.: 2.70-3.73), followed by bone involvement (ascites), RR= 1.70 (95% C. I.: 1.43-2.03). In addition, involvement of bone marrow and urinary bladder were associated with adverse survival. Involvement of muscle, subcutaneous tissue, stomach and thyroid, were associated with superior survival (Table II). Testicular involvement had no impact on overall survival.

Longitudinal Survival Analysis

By univariate Cox regression, the rate of improvement was similar for male and female patients. According to age at diagnosis, there was significant improvement (5.9-6.8% per year) in all age groups, except for the highest quartile (≥79 years) (Figure 2). Dividing the population according to IPI, significant improvement in overall survival was noted in all subgroups (Figure 3), except for the low risk group (p=0.20), and was most prominent in the high intermediate risk IPI population (5.6 % per year). There was no significant improvement in patients with poor PS (2-4). The rate of improvement was similar for patients with 0-1 or with more extra nodal sites. No improvement was seen for patients with CNS or testicular involvement, but for patients with skeletal lesions, a significant yearly improvement of 5.6% was found.

To further understand the interdependence of age and gender, the following Cox model was

adjusted: relative risk =exp(-0.11x(female gender) + 0.057 x (age at diagnosis-70)+0.000543x(age at diagnosis-70)^2 [6] where the gender term, although significant (p = 0.0069), has a rather large estimated standard deviation of 0.04. The other terms are highly significant. The quadratic correction term with positive sign means that the age effect is most pronounced in the higher age groups.

By use of the Cox model above, a substantial improvement in overall survival was noted for the group as whole during the period 2000-2013, estimated as 4.5% per year (P<0.001) (Figure 3).

Therapeutic Intent

For 4404 patients (82%) there was available information on therapeutic intent. During this decade, in total 572 patients (11%) were treated without curative intent. This fraction generally decreased during this time period in all age groups, except for the oldest (≥79 years), being 37% 2000-2005, and 32% in the later half of this decade (p=0.14). In the youngest quartile, this fraction declined from 4.2 to 1.4% from 2000-2005 to 2006-2010 (p=0.007), and was most pronounced among patients 70-78 years, 13 vs 5.4% (p<0.001).

DISCUSSION

This retrospective study is the largest population based series of DLBCL published so far, and is specifically addressing incidence patterns and temporal changes in survival, within age categories, gender, and prognostic groups and according to presentation.

The size of present study enables us to provide an even more complete picture of DLBCL on a population level, as compared to previous population based series [7-9]. The incidence of DLBCL has previously been shown to increase among men up to the year of 2000[10]. In the United States, the incidence shows a plateau during the 1990's[11]. In this series, we could document an increase also within the last decade among men, but not among women. The reason why this is restricted to males is not clear, but may be due to gender differences in exposure to environmental toxic or infectious agents.

As expected, we found age, Ann Arbor stage, number of extranodal sites, serum-LDH-level, PS, B-symptoms, and bulky disease to be statistically significant negative prognostic factors [12-14]. In addition, specific involvement of bone marrow, CNS, lung, peritoneum and skin was associated with inferior outcome. Thyroid DLBCL was the most favorable extranodal presentation in this series, with an estimated 5-year survival of 64%, in line with a recent report from the International Extranodal Lymphoma Study Group[15]. In addition, bone and muscle involvement was associated with superior survival in multivariate analyses, confirming previous reports[16,17].

In a number of series, male sex has been shown to be associated with a negative impact on OS and PFS in DLBCL, also when treated with CHOP and rituximab[9,18] [19]. One possible explanation has been provided by the German High Grade Non-Hodgkin's Lymphoma Study Group, showing that elimination half life of rituximab was significantly prolonged in women compared to men [20-22]. However, male sex has also been associated with inferior outcome in Hodgkin lymphoma, not treated with rituximab, indicating that other mechanisms may be present [23-25]. In this series, we were able to investigate the relationship of gender and age in more detail. If stratified for age, the risk for men was higher, which can be interpreted as the slightly lower median age of the men compensates for the worse prognosis. The higher risk for males was constant during the observation period, indicating that this may be unrelated to rituximab.

Note, however, that the gender effect is so small so that it is compensated for by only two years of age, implying that the risk for a 72 old woman is very close to than of a 70 old man. This means that being about two years younger compensates for the disadvantage of male sex. In the general population as whole, a woman in the upper age groups has to be three or four years older than a man to have the same death rate. (For example, the death rate 2005 for Swedish women of age 76 was 2.6 % $years^{-1}$, close to 2.7 % $years^{-1}$, which was the death rate 2005 for Swedish men aged 72. The estimated life expectancy of a 70 year old male in Sweden in 2013 is 84.6 years, compared to 87.1 years for females. Given the large standard deviation of the

gender term, it is most likely that the difference in background mortality is the cause of the effect seen in the analysis, and is most likely not a result of a gender difference in coping with the disease.

The changes in therapy during this decade are the addition of rituximab to chemotherapy[1,2,4], and the introduction of dose-dense regimens. A population based study from British Columbia showed that the addition of rituximab to anthracycline-based chemotherapy (CHOP) dramatically improved the outcome of DLBCL [26]. Dose-dense regimens, with 14-days interval with G-CSF support, as well as rituximab addition were introduced in Sweden around 2003. Other advances in the management of relapsed patients, including the use of high dose chemotherapy with autologous stem cell transplantation and improvement of supportive care, may also have contributed to the outcome during this decade.

Here we were able to show that overall survival of DLBCL has markedly improved during the last decade. The improvement was most prominent in the age group 60-78 years and for patients presenting with favourable performance status, and was significant for all IPI subgroups, except for the low risk category. Patients aged 60-78 years have to a higher degree been treated with curative intent, possibly due to the introduction of rituximab. Even patients receiving reduced chemotherapy doses may now be considered to be treated curatively, as rituximab improves efficacy without a major increase in toxicity. In contrast, survival for patients with poor PS, or age >78 years, has not significantly improved, indicating that the improvement of therapeutic regimens and supportive care has not been sufficient to overcome the adverse prognosis associated with these factors. An obvious limitation of our study was that we did not have access to data on treatment, as these data were not included in the registry until 2007. Another limitation is the lack of central pathology review, which was not feasible to perform in a cohort of this size.

In summary, this study presents a large population based cohort of DLBCL patients with detailed data on prognostic factors and outcome over time. Involvement of CNS, bone, bone marrow,

and urinary bladder, as well as male gender, were shown to be negative prognostic factors, whereas subcutaneous, gastric, muscle and thyroid involvement are associated with a superior outcome. Overall survival of these patients has markedly improved under the last decade, but to improve outcome further, our focus should be on patients with high risk features, that may benefit from upfront high dose chemotherapy, as well as on elderly patients and patients with poor performance status, that may require treatment with regimens specifically tailored for this population.

DISCLOSURE OF CONFLICTS OF INTEREST

None of the authors have any relevant conflicts of interest to disclose.

Table I

Patients' characteristics

	Number (%)
All patients	5349(100)
Gender	
Male	2919(55)
Female	2430(45)
Age	
Less than 40 years	273(5)
40-59 years	1038(19)
60-78 years	2915(50)
79 years and older	1337(25)
Missing value	26(1)
Ann Arbor Stage	
I	1052(20)
II	1286(24)
III	935(18)
IV	1893(36)
Missing value	237(4)
Extra nodal sites	
0-1	4537(85)
More than 1	812(15)
LDH-level	
Normal	2036(38)
Elevated	2970(56)
Missing	343(6)
Performance status WHO	

0-1	3812(71)
More than 1	1395(26)
Missing value	142(3)
IPI	
0	379(7)
1	1257(24)
2	1423(27)
3	1198(22)
4	557(10)
5	115(2)
Missing value	420(8)
Bulky disease	
No	3987(75)
Yes	1122(21)
Missing value	240(4)
B-symptoms	
No	2929(55)
Yes	2211(41)
Missing value	209(4)

Table II

Hazard ratios for overall survival, unadjusted and adjusted for age, gender, stage, LDH, PS and number of extranodal sites

	Univariate	Multivariate
Bone, n=407 (7.6%)	P=0.062	P<0.001
No	1(-,-)	1(-,-)
Yes	1.15(0.99,1.32)	1.70(1.43,2.03)
Bone marrow, n=634 (12%)	P<0.001	P<0.001
No	1(-,-)	1(-,-)
Yes	1.61(1.47,1.79)	1.29(1.13,1.46)
Breast, n=51 (1%)	P=0.283	P=0.337
No	1(-,-)	1(-,-)
Yes	0.81(0.55,1.19)	1.36(0.73,2.54)
CNS, n=58 (1%)	P<0.001	P<0.001
No	1(-,-)	1(-,-)
Yes	2.49(1.84,3.03)	2.18 (2.70-3.73)
Gastric, n=335 (6%)	P=0.214	P=0.042
No	1(-,-)	1(-,-)
Yes	1.10(0.95,1.27)	0.82(0.68,0.99)
Kidney, n=111 (2%)	P=0.026	P=0.915
No	1(-,-)	1(-,-)
Yes	1.32(1.04,1.70)	1.02(0.76,1.36)
Large bowel, n=150 (3%)	P=0.599	P=0.985
No	1(-,-)	1(-,-)
Yes	0.94(0.75,1.18)	1.00(0.75-1.32)
Liver, n=242 (4.5%)	P=0.001	P=0.731
No	1(-,-)	1(-,-)
Yes	1.33(1.11,1.58)	1.04(0.85,1.27)
Lung, n=259 (5%)	P<0.001	P=0.107
No	1(-,-)	1(-,-)

Yes	1.42(1.20,1.67)	1.17(0.97,1.42)
Muscle, n=111 (2%)	P=0.087	P=0.003
No	1(-,-)	1(-,-)
Yes	0.78(0.59,1.04)	0.60(0.43,0.85)
Ocular, n=11 (0.2%)	P=0.567	P=0.307
No	1(-,-)	1(-,-)
Yes	1.26(0.57,2.81)	1.81(0.58,5.69)
Ovarian, n=12 (0.2%)	P=0.693	P=0.536
No	1(-,-)	1(-,-)
Yes	0.84(0.35,2.02)	1.37(0.51,3.68)
Pancreatic, n=72 (1.3%)	P=0.006	P=0.857
No	1(-,-)	1(-,-)
Yes	1.50(1.12,1.99)	0.86(0.60,1.22)
Peritoneal, n=83 (1.6%)	P<0.001	P=0.533
No	1(-,-)	1(-,-)
Yes	1.65(1.26,2.17)	1.10(0.81,1.51)
Pleural, n=186 (3.5%)	P<0.001	P=0.187
No	1(-,-)	1(-,-)
Yes	1.55(1.29,1.86)	1.15(0.93,1.43)
Salivary gland, n=40 (0.7%)	P=0.447	P=0.887
No	1(-,-)	1(-,-)
Yes	1.17(0.79,1.77)	1.05(0.56,1.97)
Sinus, n=84 (1.6%)	P=0.739	P=0.287
No	1(-,-)	1(-,-)
Yes	0.95(0.71,1.27)	0.81(0.54,1.20)
Skin, n=155 (3%)	P=0.006	P=0.072
No	1(-,-)	1(-,-)
Yes	1.32(1.08,1.61)	1.32(0.98,1.79)
Small bowel, n=186 (3.5%)	P=0.484	P=0.961
No	1(-,-)	1(-,-)
Yes	1.07(0.88,1.30)	1.01(0.78,1.29)

Subcutaneous, n=93 (1.7)	P=0.966	P=0.049
No	1(-,-)	1(-,-)
Yes	0.99(0.75,1.31)	0.69(0.48,1.00)
Testicular, n=141 (3%)	P=0.655	P=0.688
No	1(-,-)	1(-,-)
Yes	0.95(0.76,1.19)	1.07(0.76,1.52)
Thyroid, n=67 (1.3)	P=0.028	P=0.050
No	1(-,-)	1(-,-)
Yes	0.65(0.44,0.95)	0.66(0.43,1.00)
Urinary bladder, n=33 (0.6%)	P=0.001	P=0.049
No	1(-,-)	1(-,-)
Yes	1.96(1.231,2.93)	1.60(1.00,2.57)
Uterus, n=24 (0.4%)	P=0.698	P=0.389
No	1(-,-)	1(-,-)
Yes	1.10(0.67,1.83)	0.76(0.40,1.42)
Vagina, n=8 (0.1%)	P=0.024	P=0.936
No	1(-,-)	1(-,-)
Yes	2.35(1.12,4.94)	0.96(0.36,2.59)
Other extranodal site, n=216 (4%)	P=0.742	P=0.011
No	1(-,-)	1(-,-)
Yes	0.97(0.80,1.17)	0.74(0.59,0.93)

Figure legends

Figure 1

Age-standardized incidence of diffuse large B-cell lymphoma in Sweden by year of diagnosis and gender

Figure 2

Estimated two (A) and five year (B) overall survival of diffuse large B cell lymphoma in Sweden during the period 2000-2010 according to age quartile

Figure 3

Estimated two (A) and five year (B) overall survival of diffuse large B cell lymphoma in Sweden during 2000-2010 according to International Prognostic Index.

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