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A population based study of prognostic factors and treatment in adult Burkitt lymphoma – a Swedish Lymphoma Registry study

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ABSTRACT

Burkitt lymphoma (BL) is a rare neoplasm constituting 1-2% of adult lymphomas. Our aims in this study were to establish prognostic factors for overall survival in adult BL and evaluate the efficacy of different chemotherapy regimens in a population based setting. The study population was collected from the Swedish Lymphoma Registry 2000-2010. During this period, 156 adult patients with BL were identified. In multivariate analysis, age and performance status (PS) were significant adverse prognostic factors for overall survival. A modified prognostic index, based on: age >40 years, PS >1, and LDH >ULN was proposed. Patients with a score of 0-1, 2 and 3 were found to have a 2-year survival of 91.2%, 58.4% and 27.5%, respectively. High-intensity regimens were associated with more favourable overall survival. Rituximab addition was not significantly associated with improvement in survival. A modified prognostic index may be valuable for adult BL, as proposed.

INTRODUCTION

Burkitt lymphoma (BL) is an uncommon type of mature B-cell lymphoma, constituting one to two percent of adult lymphomas in the western world. The hallmark of BL is translocation of the MYC gene to an immunoglobulin gene, turning the cell into a rapidly proliferative state [1]. Three subtypes of BL are recognised: sporadic, endemic and HIV-associated. The sporadic variant is the one most frequently seen in the western world, while the endemic variant occurs in areas where malaria is common, particularly eastern Africa. Endemic BL also arises at lower ages, most often occurring between ages two and nine, while sporadic BL can appear at any age[2]. The endemic type usually gives rise to jaw tumors, whereas sporadic BL often present as an extranodal abdominal mass. Approximately a third of patients exhibit CNS- and/or bone marrow involvement[1].

A number of prognostic factors have been described in BL, such as advanced age, advanced systemic disease, high levels of serum lactate dehydrogenase (S-LDH) >Upper Limit of Normal range (ULN), high expression of Ki-67, and CNS and/or bone marrow involvement[1,3]. The Ann Arbor staging system is typically used for adult patients, and the St. Jude/Murphy staging scheme for pediatric patients. The International Prognostic Index (IPI), is frequently used for prognostication in other aggressive lymphomas, but is not commonly used in BL[4].

Adult patients diagnosed with BL have often been subjected to less intensive therapy regimens, such as CHOP. The results with these regimens are poor, leading to adults having an inferior outcome than children given short and aggressive, high-intensive multi agent therapy with long-term survival rates of up to 90%[3]. A number of different therapy regimens have been used in adult BL, based on pediatric protocols, such as CODOX-M/IVAC [5], LMB[6]

and BFM protocols [7], or regimens designed for acute lymphatic leukemia, such as Hyper-CVAD[8]. A problem in adapting the pediatric protocols for adults is that adult patients tend to be more vulnerable to high dose methotrexate [9]. Other difficulties include a higher incidence of disseminated disease among adults as well as differences in tumour biology, such as a more complex genotype [3]. Recently, treatment with rituximab, a monoclonal antibody against CD20, frequently expressed on B-cells, has been introduced in treatment of BL, showing favorable results in comparison to historical data [8]. However, its effect in improving treatment for BL has not yet been confirmed. In adult BL, a range of studies have been performed at single centres, but no randomized trials are available, due to the rarity of this disorder. Therefore, a population based study may provide additional information concerning optimal treatment and prognostic parameters of importance. Our aims were to examine prognostic factors for overall survival in adult BL in a population-based dataset, and to analyse the therapeutic efficacy of the therapy regimens specified in the Swedish Lymphoma Registry.

MATERIALS AND METHODS

The Swedish Cancer Registry was initiated in 1958. Cases of cancer are reported to this registry in a double manner. The pathologist making the diagnosis is obliged to forward this information to the registry, a liability which the clinician also has to undertake. Due to the complexity of malignant lymphomas and their categorization the variables coded in the national cancer registry have been deemed insufficient for lymphomas. The Swedish Lymphoma group therefore initiated the Swedish Lymphoma Registry (SLR), which was set

up in 2000, including all adult patients with malignant lymphomas diagnosed within the country. Data are presented in national reports yearly. Since 2007, detailed data on treatment and response have been added to the registry. Compared to the mandatory Swedish Cancer Registry, the coverage in the SLR has been 95-97% since its initiation.

The study population covered all adult patients diagnosed with BL in Sweden from January 1, 2000 to March 31, 2010. Common criteria were applied for the diagnosis of BL. According to the national pathology guidelines, a diffuse infiltrate of medium-sized cells of B-cell phenotype, negative for TDT, and >95% expression of Ki67, with or without demonstration MYC aberration, was required for the diagnosis. The following variables from the SLR were extracted: sex, age, WHO PS, bulky disease (>10cm), B-symptoms, extranodal presentation, year of diagnosis, Ann Arbor stage, S-LDH, number of extranodal sites, immunotherapy, chemotherapy regimen, number of chemotherapy cycles, and response to primary treatment. Data regarding survival status was gathered from the Swedish Population Registry, without access to cause of death. Data on HIV status was not available.

Statistical Methods

To estimate overall survival rates the Kaplan Meier method was used. When comparing survival curves the log rank test was utilized. The hazard ratios for the various variables were calculated in univariate and multivariate analysis by Cox regression. The variables used for the multivariate analysis had all shown statistical significance for predicting overall survival with p-values of 0.05 or less in the univariate analysis. Pearson chi-square tests were computed to evaluate interrelationships among prognostic factors. All statistics were calculated in SPSS version 19.

RESULTS

Overall Patient Characteristics

The SLR contained information on 156 adult patients diagnosed with BL during the specified time period. During this period, 60 patients (38%) died. The median time of follow-up for surviving patients was 41 months. Overall patient characteristics are presented in Table I.

Prognostic Factors for Overall Survival

Interrelationships among factors

There was a clear association between higher age and poor performance status and elevated S-LDH. PS was 2 or higher in 19% of <40, 24% of the 40-59, and 52% of >60. (p=0.001). The level of S-LDH was elevated above the upper limit number in 51%, 74% and 88% of the patients in the younger, intermediate and older age group, respectively (p<0.001). Bulky disease (>10 cm) correlated with high LDH – 41% of patients with high LDH presented with bulky disease, compared to 8% in patients with normal LDH. 94% of patients with a PS of 2 or higher presented with elevated levels of LDH (compared to 64% of patients with PS 0-1). Stage and PS were also correlated – 46% of patients with PS 0-1 had stage IV disease, compared to 84% in patients with PS >1 (p<0.001). Similarly, in patients with high LDH, 74% of had stage IV disease, compared to 20% in patients with normal LDH (p<0.001). A high number of extranodal sites was associated with poor performance status (p=0.03) and higher age (p=0.03). Female gender was more often associated with inferior performance

status at presentation (49% PS 2-4) compared to men (30%) (p=0.047). Females also presented more often with bulky disease (51% vs. 26%) (p=0.01).

Age

The median age was 56 years (range 16-93 years). We stratified the study population into three groups: patients aged below 40 years, between 40 and 59 years, and 60 years and above. Age was confirmed to be a highly important prognostic factor for overall survival in both univariate and multivariate analysis (p=<0.001) with a hazard ratio (HR) of 4.5 for patients >60 years and 6.4 using >40 years as cutpoint, in the univariate analysis. Two year overall survival rates were estimated to 88% for patients <40, 77.4% for patients 40-59 years and 34.6% for patients >60 years of age. (Table II, Figure 1)

WHO performance status

Data concerning PS was available for 152/156 (97.4%). PS was a strong predictor of overall survival (p<0.001) in both univariate and multivariate analysis, with a HR of 4.4 and 2.7 respectively. 2-year survival rates were 76.9% for patients with PS 0-1 and 31.3% for patients with PS 2-4 (Table II).

S-LDH

Data was available for 94.9% of the study population (n=148). S-LDH proved statistically significant as a prognostic factor for overall survival in the univariate analysis (p=0.02) but not in the multivariate analysis. 2-year survival rates were 90.6% for patients with normal S-

LDH levels and 54.7% when S-LDH was elevated (HR=5.2). (Table II)

Gender

The majority, 72% were men (n=113) (Table II). There was a trend towards inferior overall survival among females, although not statistically significant (HR=1.7, p=0.059). 2-year survival estimates were 64.6% for men and 53.7% for women (Figure 2).

Ann Arbor stage

Data on stage was available for 145 patients (92.9%). Neither Ann Arbor stage, nor bulky disease were statistically significant predictors of survival. Two-year survival was 78.2% for stage I-II and 58.4% for patients with stage III-IV disease (HR = 1.7, p=0.092). Patients with bulky disease had a two year survival rate of 48.7%, compared to 69.1% in patients without (p=0.246) (Table II).

Number of extranodal sites

Data on extranodal involvement was available for all patients. Two-year survival was 60.3% for patients with 0-1 sites and 64.1% for patients presenting with >1 site (HR=0.8, p=0.445). The three most common extra nodal sites were bone marrow (40/156), CNS (15/156) and peritoneum (16/156). Out of these, none were confirmed to be statistically significant for overall survival in the univariate analysis (Table II).

B-symptoms

Information on the frequency of B-symptoms was reported for 149 patients (95.5%). Two-year survival rates were 70.8% in patients without and 53.6% for patients presenting with B-symptoms (HR=1.6, p=0.09) i e not statistically different (Table II).

Prognostic indices

IPI score could be calculated in 136 (87.2%) patients in our study population. The two-year survival rate was estimated to 81.3% among patients with a score of 0-2 and 51% for patients with score 3-5 (Table II, Figure 3a). To establish a prognostic index better adapted for BL, we chose to include the criteria that had proved statistically significant in the previous analysis (age > 40 years, LDH>ULN, WHO PS >1) in a 0-3 point scoring system. Subjects with a score of 0-1, 2 and 3 points were found to have a 2-year survival of 91.2%, 58.4% and 27.5%, respectively (Figure 3b).

Including LDH led to a more clear separation of the three prognostic groups. Using only two variables, age below 40 and PS below 2, estimated 2 year survival were 88%, 72% and 27%, respectively in patients with a score of 0, 1 or 2.

Year of diagnosis

Patients were stratified into two groups based on year of diagnosis. A tendency towards an improvement in survival among patients diagnosed from 2006 and onwards was noted (Figure 4). However, this improvement was not statistically significant by the log rank test (p=0.14).

Chemotherapy Regimens

Data on treatment was available for 69 patients (44.5%). Apart from a slightly lower median age (51 years) this patient cohort was representative of the whole study population regarding prognostic parameters.

BFM protocols, including BFM 90 and BFM 2004, was the most common regimen in our study population. The different regimens were administered in varying degrees to patients with different prognostic parameters (Table III). BFM was predominantly used in patients younger than 40, whereas the Hyper-CVAD regimen was predominantly administered in the intermediate age group.

Data concerning response was available for 32 patients (Table III). Of these, 12 patients received the BFM regimen, out which 91.7% achieved a complete remission (CR) and 8.3% complete remission undetermined (CRu). With Hyper-CVAD 61.5% (n=8) achieved CR, 23.1% (n=3) CRu and 15.4% (n=2) showed progressive disease (PD). The response among the few patients who received CHOP was CR in 60% (n=3) and 20% each CRu and partial remission (PR) (n=1).

The 2-year survival rates were estimated as follows: 80% for BFM, 78.6% for hyper-CVAD, 62.3% for CHOP and 33% for patients given other treatment. When dividing therapy regimens into groups of high intensity (BFM and hyper-CVAD) and low intensity (CHOP and other) treatment an HR of 3.3 (p=0.006) for overall survival was noted for patients receiving low intensity treatment. There was a trend towards inferior overall survival for patients receiving low intensity treatment even after correcting for age (p=0.054), or all three factors in the modified prognostic index, HR=0.40 (95% C. I. 0.16-1.0, p=0.056).

Rituximab was administered to 37 (53.6%) in the study population on which chemotherapy regimen was noted. Two-year survival rate was estimated to 71.1% for patients who did not receive rituximab and 74.1% for those who did. HR for overall survival was 0.8 (95% C. I. 0.5-3.0).

DISCUSSION

The aggressive nature of BL enhances the importance of prompt diagnosis and the determination of prognosis in order to initiate customized treatment. Therefore, we aimed to establish prognostic variables in a population based data set of BL, and to study the efficacy of different treatment regimens in this population.

In this series, the variables found to be of prognostic value were age, PS and to a certain degree LDH. In addition, we noted a trend towards inferior outcome among women. Ann Arbor stage and number of extra nodal sites were without prognostic impact. Moreover, presentations such as CNS or bone marrow involvement were not associated with significantly adverse prognosis.

The median age of patients in this series was 56 years, higher than previously reported [10,11]. We believe that this likely reflects the population based setting, as compared to clinical trials or single centre data. The fact that advanced age was found to be a significant prognostic factor confirms earlier literature [1 12]. The reasons for this could be more advanced disease, concomitant disease and/or poorer health in general. Also, recent studies have shown that older patients more often present with a complex BL karyotype [13], which impacts on disease

biology, response to therapy and prognosis. [14]. In our study population the survival rate differed considerably for patients aged under and over 40 years, perhaps indicating an important clinical age division for adult BL. Our results confirms those from a retrospective review of a number of treatment series of BL , where the authors found inferior overall survival for patients >40 years, although in later series, this difference was less pronounced[15].

WHO performance status was the second statistically significant prognostic factor in this series. Although there was a correlation between advanced age and higher PS, both were independent significant factors for prognosis in the multivariate analysis. A high correlation between age, PS and level of S-LDH was found, explaining why LDH failed to prove statistically significant in the multivariate analysis.

There was a trend towards impaired overall survival for female patients. This could be explained by an association with inferior performance status at presentation, and a higher frequency of bulky disease at presentation. To our knowledge, no studies have been performed regarding gender-related differences in BL disease biology or the impact of gender on BL prognosis. Our results contradict those achieved in diffuse large B-cell lymphoma (DLBCL), which have shown a worse prognosis for males [16].

Stage was not a predictor of prognosis for BL in our study, probably due to the fact that over 50% of our study population presented with Ann Arbor stage IV, implying that disseminated BL is the normal scenario rather than a sign of worse prognosis. In addition, higher stage was associated with poor performance status (PS) and elevated LDH. The lack of prognostic impact for bulky disease could be explained by a strong association with high LDH. The

number of extranodal sites was associated with PS and age. In previous reviews, extra nodal involvement of bone marrow, CNS and peritoneum was associated with an adverse prognosis [1]. These were also the most common extra nodal locations in our study population but their significance in determining prognosis could not be confirmed. This may be explained by the fact that the majority of our patients received CNS directed therapy including high-dose methotrexate.

The IPI was shown to be a solid indicator of outcome, despite the fact that IPI was developed for aggressive lymphomas in general and takes into account the Ann Arbor stage and the extent of extra nodal involvement, which were without significant prognostic value in this series. Since BL is considerably different from other aggressive lymphomas, clinically and biologically, the IPI might not be ideal for predicting overall survival for BL.

Consequently, an alternate prognostic index may be designed for BL. In our modified prognostic index we excluded the criteria from the IPI that had not proved statistically significant, and were able to distinguish three groups with even more strikingly different survival rates. These results indicate that an adapted prognostic index may serve as a valuable prognostic tool. Further population based studies with a larger patient cohort need to be performed to validate the usefulness of our adapted prognostic index.

When studying prognostic factors, we noticed a positive trend in survival based on year of diagnosis, indicating that overall survival has improved during the last decade. A limitation in this series was that data on treatment was available in less than 50% of patients. However, chemotherapy for Burkitt lymphoma has not undergone major developments during this period, 2000-2010. We therefore would anticipate that the distribution of

therapies is representative of the entire population. Concerning treatment, some interesting trends were noted. The use of more intensive therapy (BFM, hyper-CVAD) resulted in higher complete remission rates as well as higher 2-year survival rates compared to low-intensive therapies (CHOP and other), confirming the results of earlier studies [9], although the improvement in survival diminished when correcting for age. A Norwegian study showed increased CR in adolescents and adults when treated with the BFM protocol or the mmCHOP + HDT rather than the conventional CHOP regimen. The BFM protocol in turn showed better results than mmCHOP + HDT due to lower toxicity [17]. The reason for the low-intensive regimens resulting in worse outcomes, apart from being less intensive, could be that they were predominantly administered to cohorts with poorer prognosis such as older patients as well as patients presenting with poor performance status. Due to the higher toxicity with high-intensive therapy regimens, patients with these prognostic parameters were perhaps deemed to only tolerate low-intensive treatment. If that is the case, new treatment regimens need to be developed to suit the older fraction of patients with adult BL, such as previously proposed modifications of the LMB[6] and BFM protocols [18], or of the CODOX-M/IVAC regimen[11].

In our series, the highest survival rate was found with the BFM regimen. However, the BFM regimen was mainly used among patients below 40. Hyper-CVAD showed similar efficacy compared to the BFM group, but in the intermediate age group.

Regarding rituximab, our results underscore the uncertainty concerning the efficacy of rituximab in treating BL. Thomas *et al* showed an increase in CR for adults treated with a combination of rituximab and Hyper-CVAD, compared to historical data with Hyper-CVAD alone [8]. The overall survival rate for patients receiving rituximab in our study was not

significantly higher than for patients not receiving this agent. Therefore, a standardised administration of this treatment modality can be questioned until further evidence of positive effect is supplied.

Although data was collected from ten years, only 156 patients were identified in this national registry study with almost complete coverage. A clear limitation in a registry based series such as this is the wide range of pathologists and clinicians reporting to the registry and thatno central pathology review could be performed, although uniform diagnostic criteria were applied. After pathological review, is it likely that a proportion of these cases would now have been classified as B cell lymphoma unclassifiable with features intermediate between DLBCL and BL, especially in the group of patients >40 years. However, data are emerging to suggest that also patients with this lymphoma entity benefit from BL protocols such as CODOX-M/IVAC[19]. Information on MYC aberrations in the registry would have been valuable, and will be included in further developments of the registry. Another limitation in this series is that data on HIV status was not available, although, based on our experience, this is a rare entity in Sweden, and these data therefore is likely to reflect that of HIV-negative BL.

This is, to our knowledge, the first population based study of adult BL. We were able to establish age, PS-value and level of S-LDH as predictors of prognosis, and propose a disease specific prognostic index based on these factors. In the future, population based studies with a larger study population would be valuable in order to further investigate the optimal treatment of adult BL, including the value of adding rituximab.

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Table I

Characteristics of the 156 BL patients included in the Swedish lymphoma registry 2000-2010

	No. (%)
Sex	Male 113 (72%) Female 43 (27.6%)
Median age	56 (16-93)
Stage (Ann Arbor)	1- 28 (17.9%) 2- 20 (12.8%) 3- 12 (7.7%) 4- 85 (54.5%)
WHO Performance status	0- 49 (31.4%) 1- 49 (31.4%) 2- 21 (13.5%) 3- 22 (14.1%) 4- 11 (7.1%)
International Prognostic Index	0- 19 (12.2%) 1- 18 (11.5%) 2- 28 (17.9%) 3- 35 (22.4%) 4- 25 (16.0%) 5- 11 (7.1%)
No. of extranodal sites	0- 46 (29.5%) 1- 57 (36.5%) 2- 29 (18.6%) 3- 15 (9.6%) 4- 7 (4.5%) 5- 2 (1.3%)
B symptoms	76 (48.7%)
Lactate dehydrogenase >ULN	111 (71.2%)
Bulky disease (>10cm)	51 (32.7%)
Extranodal involvement	
CNS	15 (9.6%)
Bone marrow	40 (25.6%)
Peritoneum	16 (10.3%)

Table II

Estimated two-year survival and HR for prognostic factors according to univariate and multivariate Cox Regression analysis.

	Univariate analysis				**Multivariate**		
Variable (No.)	2 year survival	HR	95% CI	p-value	HR	95% CI	p-value
Age							
Below 40 years	88%						
40-59	77.4%	Age >40: 6.4	2.3-17.7	p<0.01	4.7	1.5-15.2	p=0.01
60 and above	34.6%	Age >60: 4.5	2.6-7.8	p<0.01	3.1	1.7-5.5	p<0.01
WHO performance status							
0-1 (98)	76.9%	4.4	2.6-7.4	p<0.01	3.0	1.7-5.3	p<0.01
2-4 (54)	31.3%						
LDH							
<ULN (45)	90.6%						
>ULN (111)	34.7%	5.2	1.9-14.4	p=0.02	2.5	0.9-7.2	p=0.095
International Prognostic Index							
1-2 (37)	81.3%						
3-5 (99)	51%	2.9	1.5-5.3	p=0.01			
Sex							
Male (113)	64.6%						
Female (43)	53.7%	1.7	1-2.8	p=0.059			
Stage (Ann Arbor)	78.2%						
I-II (48)	58.4%	1.7	0.9-3.3	p=0.092			
III-IV (97)							
Extranodal sites							
0-1 (103)	60.3%						
>1 (53)	64.1%	0.8	0.5-1.4	p=0.445			
Extranodal involvement							
Bone marrow	56.5%	1.2	0.7-2	p=0.586			
(40)	53.3%	1.6	0.7-3.3	p=0.249			
CNS (15)	42.2%	1.4	0.9-3.8	p=0.091			
Peritoneum (16)							
B symptoms (76)	53.6%	1.6	0.9-2.7	p=0.088			

Bulky disease(51)	48.5%	1.3	0.9-1.93	p=0.246

Table III

Distribution of chemotherapy regimens in relation to prognostic factors and outcome.

Group	(total No.)	BFM (tot %)	Hyper-CVAD	CHOP	Other
Total with treatment:	**(69)**	36 (52.2%)	15 (21.7%)	12 (17.4%)	6 (8.7%)
Sex					
Male	**(51)**	25 (69.4%)	11 (73.3%)	11 (91.7%)	4 (66.7%)
Female	**(18)**	11 (30.6%)	4 (26.7%)	1 (8.3%)	2 (33.3%)
Age					
<40	**(21)**	17 (47.2%)	1 (6.7%)	3 (27.3%)	0
40-59	**(29)**	15 (41.7%)	8 (53.3%)	3 (27.3%)	3 (50%)
60+	**(18)**	4 (11.1%)	6 (40%)	5 (45.5%)	3 (50%)
Lactate dehydrogenase levels					
< ULN	**(17)**	12 (35,3%)	1 (6,7%)	3 (25%)	1 (16,7%)
> ULN	**(50)**	22 (64,7%)	14 (93,3%)	9 (75%)	5 (83,3%)
WHO performance status					
0-I	**(50)**	25 (71.4%)	14 (100%)	7 (63.6%)	4 (66.7%)
II-IV	**(16)**	10 (28.6%)	0	4 (36.4%)	2 (33.3%)
Stage (Ann Arbor)					
I-II	**(22)**	13 (36.1%)	5 (33.3%)	3 (25%)	1 (16.7%)
III-IV	**(47)**	23 (63.9%)	10 (66.7%)	9 (751%)	5 (83.8%)
Outcome					
CR		11 (91.7%)	8 (61.5%)	3 (60%)	1 (50%)
CRu		1 (8.3%)	3 (23.1%)	1 (20%)	0
PR		0	0	1 (20%)	0
PD		0	2 (15.4%)	0	1 (50%)
2 year Overall Survival		80%	78.6%	62.3%	33%

FIGURE LEGENDS

Figure 1

Overall survival for adult BL patients in Sweden 2000-2010 according to age at diagnosis.

Figure 2

Overall survival for adult BL patients in Sweden 2000-2010 grouped according to gender.

Figure 3

Overall survival for adult BL patients in Sweden 2000-2010 grouped according to IPI (a) and according to the modified prognostic index (b).

Figure 4

Overall survival for adult BL patients in Sweden 2000-2010 grouped according to year of diagnosis.