ORIGINAL ARTICLE

Lack of prognostic significance of the germinal-center phenotype in diffuse large B-cell lymphoma patients treated with CHOP-like chemotherapy with and without rituximab

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Abstract The influence of the germinal-center B-cell (GCB) and the non-GCB phenotypes of diffuse large B-cell lymphoma (DLBCL) on the outcome of 92 patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy, with or without rituximab was determined in this study. The differentiation between the GCB and non-GCB types was arrived at by immunohistochemistry using previously published criteria. Thirty-nine patients had the GCB and 53 had the non-GCB type of DLBCL. Forty-nine patients were treated with rituximab and chemotherapy; 43 were treated with chemotherapy alone. The GCB and non-GCB group did not differ in their international prognostic index factors and score, presence of bulky disease, or frequency of rituximab treatment. Median follow-up of the surviving patients was carried out for 37 months. There was no difference between the GCB and non-GCB groups in both overall response rates (67 vs. 70%, respectively) and estimated rates of 3-year event-free (46 vs. 49%, respectively) and overall (54 vs. 56%, respectively) survival. In addition, no differences of the outcomes were observed between the subgroups treated with or without rituximab. The patients of this study with immunohistochemically determined GCB-type DLBCL did not have an improved prognosis, irrespective of whether they had received rituximab or not.

Keywords Lymphoma, non-Hodgkin · Lymphoma, large B-cell, diffuse · Immunohistochemistry · Rituximab · CHOP chemotherapy

1 Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL) accounting for about 30% of all NHL cases [1, 2]. It is treated with anthracycline-based chemotherapy that comprises a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or similar so-called CHOP-like regimens. The addition of a monoclonal anti-CD20 antibody, rituximab (R), to CHOP led to a significant improvement in the outcome of patients with DLBCL, establishing R–CHOP as the new standard treatment [3, 4]. Based on the diversity of the clinical, morphologic, molecular, and genetic characteristics of DLBCL, many researchers consider this disease as a spectrum of several entities [5]. Throughout the past several years, the identification of more aggressive subtypes of DLBCL with inferior prognosis, which may benefit from more intensive treatment, has been a constant challenge for researchers. In 1993, the international prognostic index (IPI) was introduced as a new and independent prognostic factor [6]. Very soon, IPI became a golden prognostic standard worldwide and remains as such until today. IPI is based on clinical and laboratory parameters: age, lactate dehydrogenase (LDH) levels, number of involved extranodal sites, performance

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status, and clinical stage. Numerous potential prognostic parameters were analyzed during the last several decades; however, none of them, clinical or molecular, was found to be consistently associated with the prognosis of DLBCL.

In 2000, Alizadeh et al. [7] analyzed the expression of several hundred genes to identify different subtypes of DLBCL. They defined three distinct types of DLBCL: germinal-center B-cell-like (GCB), activated B-cell-like (ABC), and a "third type" that did not fit into either of the two previous categories. The latter group was later merged with the ABC group into a non-GCB group because of the similarities in biological behavior and survival between them. Their study showed not only that the GCB and ABC types are histogenetically different, but also that they have different biological behaviors, with a significantly better outcome for the patients with the GCB subtype. This effect was independent of the IPI. The usefulness of gene-expression profiling for the subtyping of DLBCL has been confirmed by several other authors [8–10]. Hans et al. [11] proposed the use of immunohistochemistry for the identification of the GCB and non-GCB subtypes of DLBCL by determining the protein expression of CD10, BCL6, and MUM1 in tumor cells. The prognostic impact of immunohistochemical subtyping into GCB and non-GCB subtypes has been confirmed in some [12–16], but not in all [17–19], studies. Several recent studies have shown that the differences in survival between the groups disappeared if the DLBCL patients were treated with immunochemotherapy, i.e. CHOP-like chemotherapy combined with rituximab [16, 17]. Considering the conflicting results of previous studies and the possible effect of rituximab on differences in survival rates, this study was carried out to determine the influences of both GCB and non-GCB phenotypes on the outcomes of DLBCL patients treated with CHOP or CHOP-like chemotherapy with or without addition of rituximab.

2 Materials and methods

2.1 Patients

This was a retrospective cohort study conducted on 92 patients with de novo and previously untreated DLBCL diagnosed and treated at our institutions. Inclusion criteria were as follows: confirmed diagnosis of DLBCL by two pathologists, availability of diagnostic paraffin block, sufficient amount of tissue in the paraffin block for additional testing, clinical stage 2 or more and front-line treatment with an anthracycline-based chemotherapy regimen. Exclusion criteria were incomplete clinical data, treatment with nonanthracycline-based chemotherapy, clinical stage I, HIV-associated lymphoma, transformed indolent lymphoma, and presence of composite lymphoma. Patients diagnosed before the year 2001 were treated only with standard chemotherapy, whereas those diagnosed later received standard chemotherapy in combination with rituximab. Chemotherapy regimens included CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone), COP-BLAM (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin, and procarbazine), BACOP (cyclophosphamide, doxorubicin, vincristine, bleomycin, and prednisone), or EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone). Among the patients, 49 were treated additionally with a dose of rituximab (43 patients with R–CHOP, 2 patients with R–CNOP, and 4 patients with R–EPOCH), whereas 43 did not receive rituximab in their treatment. Out of those who did not receive rituximab, 30 were treated with CHOP and 13 were treated with a CHOP-like regimen that included 7 patients with ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), 2 with CNOP, and 4 with COP-BLAM.

Patients with bulky disease at introduction were routinely irradiated after the end of chemotherapy. A tumor was considered bulky if its largest diameter was 7.5 cm or more. Data on the gender, age, clinical stage, LDH level, tumor size, number of extranodal sites involved, treatment, and its outcome were obtained from the patient's medical history.

The study was approved by the Ethics Committee of Medical School, University of Zagreb, Croatia. Patients were not contacted directly because of the retrospective nature of the study.

2.2 Immunohistochemical staining and analysis

All biopsy specimens were reviewed by two hematopathologists and were classified according to the criteria proposed by the World Health Organization (WHO) [1].

Fresh 4-μm-thin sections were obtained from the paraffin-embedded tissue. The slides were stained with hematoxylin and eosin to confirm the presence of tumor. The material was immunohistochemically stained with antibodies against CD20 (clone L26, 1:200 dilution, Dako, Glostrup, Denmark), CD3 (clone PC3/188A, 1:50 dilution, Dako, Glostrup, Denmark), CD10 (clone 56C6, 1:20 dilution, Novocastra, UK), BCL6 (clone P1F6, 1:20 dilution, Novocastra, UK), and MUM1 (clone MUM1p, 1:100 dilution, DAKO, Denmark) using the avidin–biotin method. In accordance with previous studies, tumors were considered positive if 30% or more of the tumor cells stained positive [11]. Immunohistochemical characteristics were used to identify the subtype of the patients as the GCB or non-GCB group, according to previously published criteria [11].

2.3 Statistical analysis

The χ^2 test was used for the comparison of clinical characteristics (gender, age, clinical stage, LDH level, tumor size, number of extranodal sites involved, IPI, treatment regimen, and response to treatment) between the GCB and non-GCB patients. The Kaplan–Meier method was used for the construction of survival curves. Log-rank test was used for the assessment of differences between groups in terms of event-free (EFS) and overall (OS) survival. The EFS was calculated from the date of diagnosis until the failure of treatment or the last follow-up. Failure to achieve complete remission or unconfirmed complete remission with the initial treatment, institution of unplanned anti-lymphoma treatment, and relapse or death from any cause were considered treatment failures. OS was calculated from the date of diagnosis to the date of the last follow up or death. Patients who did not reach endpoints were censored.

Statistica 7.0 software (StatSoft Inc., Tulsa, OK, USA) was used for data analysis. A P value of less than 0.05 was considered significant.

3 Results

The demographic and clinical characteristics of the patients evaluated are shown in Table 1. Among these, 49 (42%) patients had GCB and 53 (58%) had non-GCB type of DLBCL. Forty-three (47%) patients received only chemotherapy and 49 (53%) patients received chemotherapy plus rituximab. The GCB and non-GCB groups did not differ in their demographic characteristics, IPI factors and score, presence of bulky disease, chemotherapy regimens, and treatment with rituximab. Twenty-nine (32%) DLBCLs were CD10-positive, 54 (59%) were BCL6-positive, and 49 (53%) were MUM1-positive (Table 2) cases. The expression of any single of these markers did not correlate with the response to treatment or the overall survival (Table 2).

Thirty-seven patients died during the researched period. The median follow-up duration of the survivors was 37 months (range 4–105 months).

Response to the front-line treatment was evaluated according to standard criteria [20]. Out of 92 patients, 66 (69%) patients showed a complete response (CR), 13 (16%) had a partial response, and 13 (16%) failed to respond to the front-line treatment. Twenty-six patients (67%) in the GCB group and 37 (70%) in the non-GCB group achieved CR ($P = 0.999$). The 3-year OS of all patients was $55 \pm 6\%$, and the 3-year EFS for the same group of patients was $47 \pm 5\%$. The 3-year EFS was $46 \pm 8\%$ for the GCB group of patients and $49 \pm 7.0\%$ for the non-GCB group ($P = 0.962$) (Fig. 1a). The 3-year OS was $54 \pm 9\%$ for the GCB group and $56 \pm 7\%$ for the non-GCB group ($P = 0.685$) (Fig. 1b).

The outcomes were also analyzed separately for the patients treated with and without rituximab. In the group treated with standard chemotherapy alone, 9 patients (60%) with GCB DLBCL and 17 (61%) patients with non-GCB DLBCL achieved CR ($P = 0.749$). The 3-year EFS was $40 \pm 13\%$ for the GCB group and $40 \pm 9\%$ for the non-GCB group ($P = 0.469$) (Fig. 2a). The 3-year OS was $60 \pm 13\%$ for patients with GCB DLBCL and $45 \pm 10\%$ for patients with non-GCB DLBCL ($P = 0.182$) (Fig. 2b).

Among the patients treated with rituximab, 17 patients (71%) in the GCB group and 20 (80%) in the non-GCB group achieved CR ($P = 0.736$). The 3-year EFS of GCB patients was $52 \pm 11\%$ and that of non-GCB patients was $58 \pm 10\%$ ($P = 0.488$) (Fig. 3a). The 3-year OS was $58 \pm 11\%$ for GCB patients and $69 \pm 10\%$ for non-GCB patients ($P = 0.481$) (Fig. 3b).

4 Discussion

The results of this study showed that patients with the GCB subtype of DLBCL have an outcome similar to that of patients with the non-GCB subtype. This was found in the group of patients treated with rituximab and in those treated during the prerituximab era. The lack of differences in the outcomes cannot be explained by differences in clinical risk factors, such as the IPI or presence of bulky disease, because these factors were balanced well between the groups.

Table 1 Analysis of CD10, BCL6 and MUM1 and their influence on survival and treatment response

Immunohistochemical marker	Number (percentage) of DLBCL with expression	Survival impact (Kaplan–Meier test) P value	Treatment response (χ^2 test) P value
CD10	29 (32%)	0.388	0.999
BCL6	54 (59%)	0.479	0.098
MUM1	49 (53%)	0.429	0.643

Table 2 Demographic and clinical characteristics of 92 patients with diffuse large B-cell lymphoma with germinal center like phenotype (GCB) and non-germinal center like phenotype (non-GCB)

	N = 92 (%)	GCB (N = 39)	Non-GCB (N = 53)	P value
Gender				
Female	51 (55)	20 (51)	31 (59)	0.530
Male	41 (45)	19 (49)	22 (41)	
Age				
Median (range)	51 (16–78)			
<60 years	62 (67)	29 (74)	33 (62)	0.265
≥60 years	30 (33)	10 (26)	20 (38)	
Clinical stage				
II	29 (32)	13 (33)	16 (30)	0.946
III	10 (11)	4 (10)	6 (11)	
IV	53 (58)	22 (56)	31 (59)	
LDH				
Normal	29 (32)	14 (36)	15 (28)	0.499
Elevated	63 (68)	25 (64)	38 (72)	
Tumor size				
Non bulky	50 (54)	18 (46)	32 (60)	0.380
Bulky	35 (38)	16 (41)	19 (36)	
Unknown	7 (8)	5 (13)	2 (4)	
Extranodal sites				
<2 extranodal sites	64 (70)	26 (67)	38 (72)	0.651
≥2 extranodal sites	28 (30)	13 (33)	15 (28)	
IPI				
0–2	52 (57)	21 (54)	31 (58)	0.676
3–5	40 (43)	18 (46)	22 (42)	
Rituximab				
Administered	49 (53)	24 (62)	25 (47)	0.139
Not administered	43 (47)	15 (38)	28 (53)	
Chemotherapy				
CHOP	73 (79)	31 (34)	42 (45)	0.795
CHOP-like	19 (21)	7 (8)	12 (13)	
CNOP	4 (4)	3 (3)	1 (1)	
EPOCH	4 (4)	2 (2)	2 (2)	
BACOP	7 (8)	2 (2)	5 (5)	
COP-BLAM	4 (4)	0 (0)	4 (4)	

GCB germinal center like phenotype, *LDH* lactate-dehidrogenase, *IPI* international prognostic index, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednison, *CNOP* cyclophosphamide, mitoxantrone, vincristine, prednisone, *EPOCH* etoposide, cyclophosphamide, doxorubicine, vincristine, prednisone, *BACOP* bleomycin, cyclophosphamide, doxorubicine, vincristine, prednisone, *COP-BLAM* bleomycin, procarbazine, cyclophosphamide, mitoxantrone, vincristine, prednisone

Although this study is a retrospective one and the patients were diagnosed and treated over a prolonged period with different chemotherapy regimens, the authors do not consider that these facts accounted for the observed results. Since the introduction of CHOP in the early 1970s, no further major improvement in the outcome of DLBCL patients occurred until the introduction of rituximab [2]. Although a number of different chemotherapy regimens were used during this period, the only four that were superior to CHOP in randomized trials (CHOP14, CHEOP, ACVBP, and CEOP–IMVP) were not used in the authors' treatment centers. Furthermore, treatment regimens and periods were well balanced between the GCB and 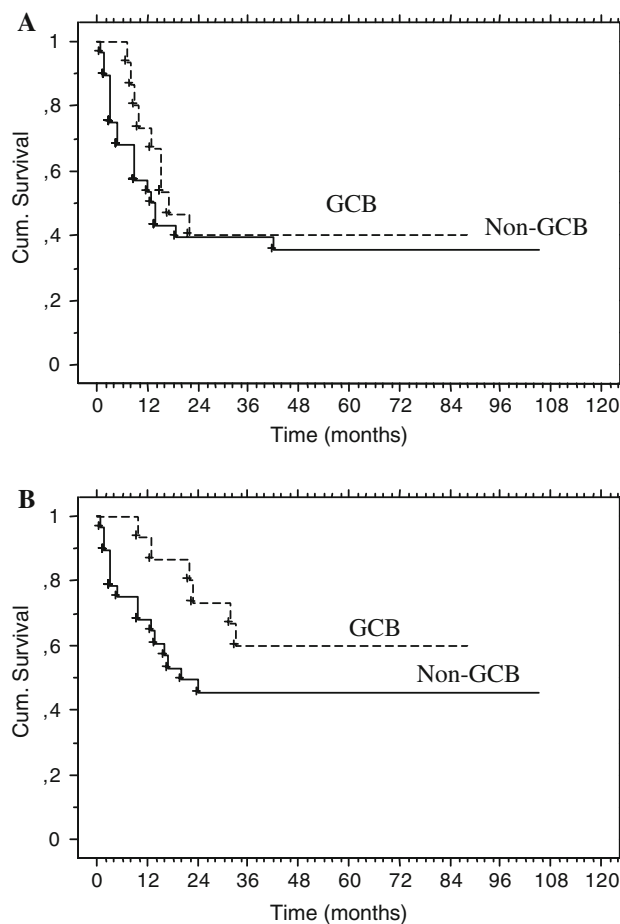non-GCB groups. The outcome cannot be explained by inadequate pathologic evaluation, because all the cases were reviewed by two experienced hematopathologists and the subtype was only assigned after a consensus was reached. The frequencies of CD10-, BCL6-, and MUM1-positivity were similar to those in other published studies [17–22]. Of the DLBCL cases, 42% were identified to belong to the GCB subtype. This frequency is in accordance with the results of other studies using immunohistochemistry [11–22] but slightly less than that identified using gene-expression profiling [7–10]. The lack of difference was probably also not due to a small sample size. The number of patients in this study was similar to that in other published series, and there was no indication of benefit for any of the outcomes or subgroups analyzed.
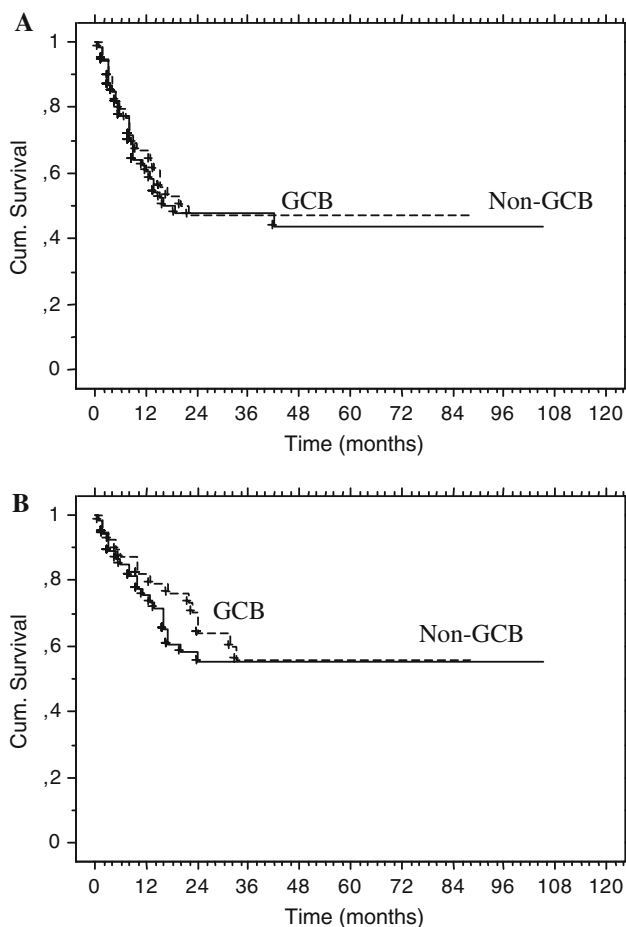
Fig. 1 **a** Event-free survival of patients with germinal center (*dashed line*) and non-germinal center type (*continuos line*) of diffuse large B-cell lymphoma (*P* = 0.781). **b** Overall survival of patients with germinal center (*dashed line*) and non-germinal center type (*continuos line*) of diffuse large B-cell lymphoma (*P* = 0.549)

Fig. 2 **a** Event-free survival of patients with germinal center (*dashed line*) and non-germinal center type (*continuos line*) of diffuse large B-cell lymphoma treated with chemotherapy without rituximab (*P* = 0.469). **b** Overall survival of patients with germinal center (*dashed line*) and non-germinal center type (*continuos line*) of diffuse large B-cell lymphoma treated with chemotherapy without rituximab (*P* = 0.182)

Moreover, the difference noted in the initial studies was sufficiently large to be reliably detected with even a lesser number of patients than that considered herein [7, 11].

Although there is a consensus that DLBCL cases can be reliably divided into the GCB and non-GCB subtypes based on gene-expression profiling and that this difference has a prognostic significance, the same is not true for immunohistochemical differentiation as described by Hans et al. The authors were able to retrieve five published studies from other centers reporting results similar to those of Hans et al. (although in one study, this was true only for the group of patients not receiving rituximab) [12–16] and four studies reporting diametrically opposite results [17–19, 22]. The study from the Memorial Sloan-Kettering Cancer Center included only patients receiving salvage therapy [17], but the Spanish [18] and German [19] studies included only previously untreated patients. Therefore, the herein-presented results are similar to those obtained by the latter two groups. The authors are unable to explain this

discrepancy. It does not appear to be only due to the differences in treatment with rituximab because the group that conducted the initial study found that, in their institution, treatment with rituximab did not annul the prognostic influence of the immunohistochemical DLBCL classification [21].

It is obvious that the Hans method of classifying DLBCL immunohistochemically into the GCB and the non-GCB types has several failures and that the three markers proposed in that method are not sufficient. A few studies showing that there was a survival difference between the GCB and the non-GCB groups are probably the result of a higher expression of BCL6 in the GCB subgroup. BCL6 has been associated with a better prognosis even in those studies showing no correlation of the prognosis with the DLBCL subtypes [22]. CD10, which is one of the two hallmarks of the GCB subtype, has not
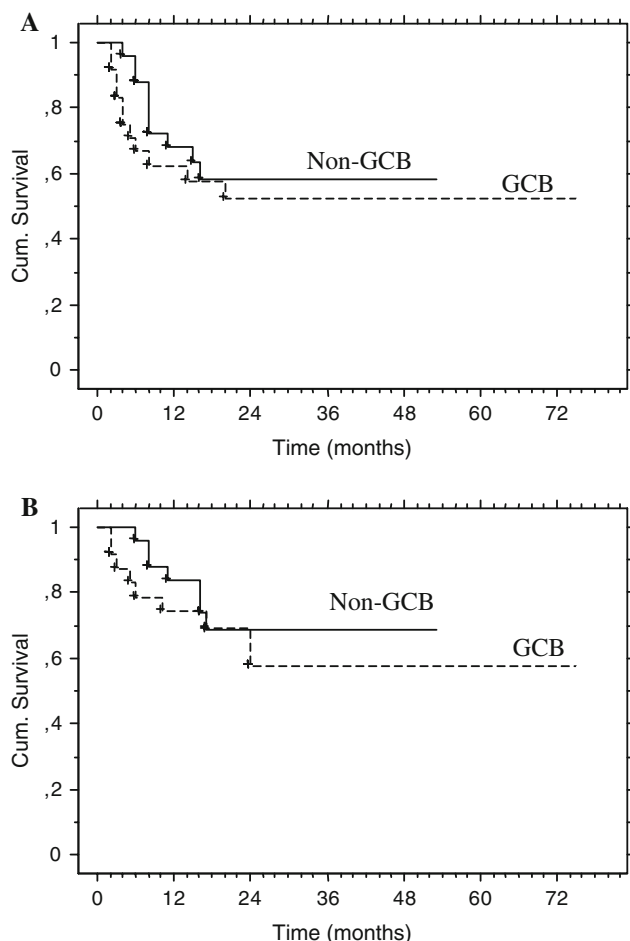
Fig. 3 a Event-free survival of patients with germinal center (*dashed line*) and non-germinal center type diffuse large B-cell lymphoma (*continuos line*) treated with R–CHOP ($P = 0.488$). **b** Overall survival of patients with germinal center (*dashed line*) and non-germinal center type of diffuse large B-cell lymphoma (*continuos line*) treated with R–CHOP ($P = 0.481$)

shown consistent results until now in predicting the outcome of this dreaded disease [23].

The differences in the results of different study groups and the fact that the number of GCB cases identified by immunohistochemistry is less than that identified by gene-expression profiling indicate that these two methods are not equivalents. Until the reasons for the reported differences in the outcomes of patients with immunohistochemically determined GCB and non-GCB subtypes of DLBCL are identified, this classification should not be used to guide clinical decisions regarding their treatment.

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