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Prognostic significance of the number and type of extra nodal localizations of DLBCL in the rituximab era

Znaczenie prognostyczne liczby zmian pozawęzłowych oraz typu zajętego narządu u chorych na DLBCL w dobie leczenia rytuksymabem

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ABSTRACT

Introduction: The aim of the study was to assess the prognostic significance of the number and type of extra nodal localizations of DLBCL as well as other factors included in IPI in the rituximab era. **Materials and methods:** We conducted a retrospective analysis of medical documentation of 178 patients with DLBCL treated in two oncology centers between 2006 and 2011. We distinguished 3 subgroups of patients: with only nodal localization of DLBCL (A, $n = 80$), with 1 extra nodal site (B, $n = 66$) and with ≥ 2 extra nodal sites (C, $n = 32$). **Results:** The presence and the number of extra nodal lesions did not have a prognostic impact both on the response and survival. Probabilities for OS were 79.4% $\pm$ 6, 85.5% $\pm$ 5 and 78.5% $\pm$ 8 for groups A, B and C respectively. Most common extra nodal localizations of DLBCL were: digestive duct, bones and skin. The site of involvement also did not have a prognostic significance. In a multivariate analysis negative prognostic factors for OS probability were: elevated LDH level (HR: 3.12 [95% CI: 1.3–7.47], $p = 0.01$) and disease stage $\geq$III (HR: 4.61 [95% CI: 1.32–16.1], $p = 0.02$). **Conclusions:** Neither the number of extra nodal lesions nor their localization affects prognosis in patients with DLBCL in the rituximab era.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma among adults, accounting for 25–50% of cases [1, 2]. DLBCL is a heterogeneous disease, with multiple morphologic variants and histological subtypes [1–3]. We can distinguish, inter alia, nodal and primary extra nodal disease [1]. For last few decades CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen was the gold standard of care in case of DLBCL [4]. Attempts to improve outcomes by adding other cytostatic agents to this regimen or changing dose intensity failed to show long-term benefit with increased toxicity of such treatment [5–10]. Adding rituximab, a monoclonal antibody targeting CD20, to CHOP chemotherapy led to significant improvement of treatment outcomes with acceptable toxicity in elderly (≥60-years-old) as well as younger (18–60-years-old) patients with low risk according to age adjusted IPI (aaIPI) [11–14]. R-CHOP immunochemotherapy is to date the mainstay of therapy in patients suffering from DLBCL, although its role in case of extra nodal disease is controversial [3, 15–18].

Despite these promising outcomes, about 30% of patients still experience DLBCL relapse [3, 19, 20]. Patients not cured by the first-line therapy have significantly worse prognosis and early identification of these poor-risk patients may lead to alternate treatment strategies consideration [21]. International Prognostic Index (IPI) was the first tool to predict outcome for patients with DLBCL [20]. According to IPI we distinguish four outcome groups and negative prognostic factors are: age > 60, clinical stage of the disease III/IV according to Ann-Arbor classification, elevated lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥2 and ≥2 extra nodal sites of the disease. For patients younger than 60 years age adjusted IPI (aaIPI), based on three risk factors (CS III/IV, elevated LDH and ECOG-PS ≥2) was applied. IPI was designed before rituximab era and, in the face of more effective treatment, its utility is a matter of debate [22]. For patients treated with immunochemotherapy revised IPI (R-IPI), which identifies three outcome groups, was created [21]. Neither IPI nor R-IPI identifies a group of patients with less than 50% chance of survival [20, 21]. New prognostic markers defined by gene expression profiling are still not helpful in therapeutic decision making [3].

The aim of this study was to assess the prognostic significance of the number and type of extranodal localizations as well as other factors included in IPI in the rituximab era.

Materials and methods

Study design

We conducted a retrospective analysis of an unselected population of patients treated in Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch and Franciszek Łukaszczyk Memorial Cancer Center in Bydgoszcz between 2006 and 2011. Inclusion criteria were: newly diagnosed, histologically proven DLBCL, patient's age above 18 years and first-line treatment with R-CHOP regimen administered at a 21-day interval. Patients suffering from primary central nervous system lymphoma, primary mediastinal B-cell lymphoma or with incomplete documentation were excluded. Response to treatment was evaluated according to The International Workshop Criteria 1999 [23].

Patient characteristics

On the basis of above mentioned criteria we identified 178 eligible patients. No dose reduction was noted. The median time of observation was 21 months. Clinical characteristics of patients at diagnosis are listed in Table I.

We distinguished three subgroups of patients – with only nodal involvement (group A; $n = 80$), with 1 extra nodal site of the disease (group B; $n = 66$) and with 2 and more extra nodal sites of DLBCL (group C; $n = 32$).

Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis until death of any cause or date last known alive.

Table I – Patient's clinic pathological characteristics
Tabela I – Charakterystyka chorych

Median age (range)	57 (20–80) years
Age > 60	73 (41%)
Gender	
M	88 (49.4%)
F	90 (50.6%)
Clinical stage	
I	41 (23%)
II	37 (20.8%)
III	42 (23.6%)
IV	58 (32.6%)
B-symptoms	77 (43.3%)
ECOG-PS	
0	66 (37.1%)
1	76 (42.7%)
2	31 (17.4%)
3	5 (2.8%)
4	0
Number of extranodal lesions	
0	80 (44.9%)
1	66 (37.1%)
2	17 (9.5%)
3	11 (6.2%)
4	3 (1.7%)
5	1 (0.6%)
Median Ki67	80% (20–100)
Radiotherapy after 1st line treatment	47 (26.4%)
IPI	
0	36 (20.2%)
1	48 (27%)
2	47 (26.4%)
3	29 (16.3%)
4	14 (7.9%)
5	4 (2.2%)
Relapse/progression	33 (18.5%)

ECOG-PS – Eastern Cooperative Oncology Group Performance Status; IPI – International Prognostic Index.

Progression free survival (PFS) was calculated from the date of achieving CR/CRu until disease progression, patient death or date last known alive. Event free survival (EFS) was calculated from the date of diagnosis until one of the following events: disease progression, not reaching complete remission/uncertain complete remission (CR/CRu), death of any cause or date last known alive. OS, PFS and EFS were estimated by the Kaplan–Meyer method. For a multivariate analysis we used the Cox proportional hazards model.

The response rates were compared using Fisher's exact test. For a multivariate analysis logistic regression was used.

Results

Prognostic significance of the number of extra nodal localizations

The presence and the number of extra nodal localizations did not have a prognostic impact on neither treatment response nor survival. 62 (81.6%) of patients with only nodal involvement achieved CR or CRu in comparison with 45 (65.2%) patients with one extra nodal site involved ($p = 0.03$) and 21 (63.6%) patients with two or more extra nodal sites of DLBCL ($p = 0.05$). Among patients with no extra nodal site of the disease 6 (7.9%) experienced progression after immunochemotherapy in comparison to 5 (7.2%) patients with one extra nodal site involved ($p = 0.5$) and 4 (12.1%) patients with two or more extra nodal sites ($p = 0.49$). OS probability at 3 years of observation was 79.8% ± 6 among patients with only nodal presentation of DLBCL in comparison to 83% ± 5 among patients with one extra nodal DLBCL localization ($p = 0.71$) and 79.3% ± 7 in patients with more than one extra nodal site involved ($p = 0.42$). More detailed data concerning the prognostic impact of the presence and number of extranodal sites on treatment response and survival are presented in Table II.

Prognostic significance of the type of extra nodal localizations

Three most commonly involved extra nodal sites were digestive duct (stomach, small and large intestine), bones and skin. Patients with DLBCL involving digestive duct achieved CR or CRu in 66.7% (28 patients), whereas we noted CR/CRu in 14 (53.8%) patients with bone involvement ($p = 0.31$) and in 12 (66.7%) patients with skin localization ($p = 1.00$). Disease progression occurred in 3 (7.1%) patients diagnosed with digestive duct involvement in comparison to 1 (3.8%) patient with bones involvement ($p = 1.00$) and 4 (22.2%) patients with DLBCL of the skin ($p = 0.18$). OS probability at 3 years of observation was 77.6% ± 7 in patients with DLBCL of the digestive duct in comparison to 86% ± 7 in patients with bone lesions ($p = 0.8$) and 78.7% ± 11 among patients with DLBCL of the skin ($p = 0.99$). The type of involved organ did not have a prognostic impact (Table III).

Prognostic significance of factors included in IPI

In a univariate analysis elevated LDH level negatively affected response rates, OS and EFS (Table IV). We observed CR or CRu in 85 (79.4%) patients with LDH level within the standard and in 43 (60.6%) patients with elevated LDH level ($p = 0.01$). Moreover, significantly more patients with elevated LDH level experienced disease progression – 12 (16.9%) vs. 3 (2.8%) with LDH level within the standard ($p = 0.001$). OS probability at 3 years of observation was 92.3% ± 3 among patients with normal LDH level vs. 61.7% ± 8 in patients with elevated LDH level ($p = 0.0004$). A similar correlation was observed for EFS probability (77% ± 4.6 vs. 51.6% ± 7.5; $p = 0.003$) but not PFS probability (87.6% ± 5 vs. 82% ± 8.5; $p = 0.43$). In univariate analysis patients with poor performance status (ECOG-PS ≥ 2) rarely achieved CR/CRu in comparison to patients with ECOG-PS < 2 (20 (55.5%) vs. 108 (76.1%); $p = 0.02$) and more often experienced disease progression (7 (19.4%) vs. 8 (5.6%); $p = 0.01$). Moreover, OS probability at 3 years of observation was significantly lower among patients with ECOG-PS ≥ 2 in comparison to patients with ECOG-PS > 2 (68% ± 8.5 vs. 84% ± 4.2; $p = 0.008$) as well as EFS probability (48% ± 9.5 vs. 42.5% ± 4.4; $p = 0.004$) and PFS probability (70% ± 13.6 vs. 89% ± 4.6; $p = 0.03$). Also patients with advanced disease stage (III or IV) more often experienced disease progression in comparison to patients with DLBCL at stage I or II (14 (14%) vs. 1 (1.3%); $p = 0.002$). They also rarely achieved CR/CRu (62 (62%) vs. 66 (84.6%); $p = 0.01$). OS probability at 3 years of observation was

Table II – The prognostic impact of the presence and number of extra nodal sites on treatment response and survival
Tabela II – Znaczenie prognostyczne obecności i liczby zmian pozawęzłowych dla odpowiedzi na leczenie i przeżycia

	Only nodal involvement (A) $n = 80$	1 extra nodal site (B) $n = 66$	≥2 extra nodal sites (C) $n = 32$	p (A vs. B)	p (A vs. C)	p (B vs. C)
CR	48 (63.1%)	38 (55%)	15 (45.4%)	0.39	0.09	0.4
CRu	14 (18.4%)	7 (10.1%)	6 (18.2%)	0.23	1.00	0.34
CR+CRu	62 (81.6%)	45 (65.2%)	21 (63.6%)	0.03	0.05	1.00
PR	5 (6.6%)	15 (21.7%)	7 (21.2%)	1.00	0.75	0.76
CR+CRu+PR	67 (88%)	60 (86.9%)	28 (84.8%)	0.014	0.04	1.00
SD	3 (3.9%)	4 (5.8%)	1 (3%)	0.7	1.00	1.00
PD	6 (7.9%)	5 (7.2%)	4 (12.1%)	0.5	0.49	0.46
OS (%, ±SE)	79.8 ± 6	83 ± 5	79.3 ± 7	0.71	0.42	0.54
EFS (%, ±SE)	69 ± 6	65 ± 6	68.1 ± 8	0.21	0.19	0.7
PFS (%, ±SE)	71 ± 6	72 ± 5.8	55.6 ± 14	0.72	0.35	0.53

CR – complete remission; Cru – uncertain complete remission; PR – partial response; SD – stable disease; PD – progressive disease; OS – overall survival; EFS – event free survival; PFS – progression free survival; SE – standard error.

Table III – The prognostic impact of the type of extra nodal sites on treatment response and survival
Tabela III – Znaczenie prognostyczne typu zajętego narządu pozawęzłowego dla odpowiedzi na leczenie i przeżycia

	Digestive duct (A) $n = 42$	Bones (B) $n = 26$	Skin (C) $n = 18$	p (A vs. B)	p (A vs. C)	p (B vs. C)
CR	22 (52.4%)	10 (38.5%)	10 (55.5%)	0.32	1.00	0.36
CRu	6 (14.3%)	4 (15.4%)	2 (11.1%)	1.00	1.00	1.00
CR+CRu	28 (66.7%)	14 (53.8%)	12 (66.7%)	0.31	1.00	0.53
PR	9 (21.4%)	9 (34.6%)	1 (5.5%)	0.27	0.25	0.03
CR+CRu+PR	37 (88.1%)	23 (88.5%)	13 (72.2%)	1.00	0.15	0.24
SD	2 (4.8%)	2 (7.7%)	1 (5.5%)	0.63	1.00	1.00
PD	3 (7.1%)	1 (3.8%)	4 (22.2%)	1.00	0.18	0.14
OS (%, ±SE)	77.6 ± 7	86 ± 7	78.7 ± 11	0.8	0.99	0.97
EFS (%, ±SE)	68 ± 7.3	54 ± 11.4	56.6 ± 12.7	0.58	0.53	0.83
PFS (%, ±SE)	88.9 ± 10.5	88.9 ± 10.5	90 ± 9.5	0.44	0.87	0.87

CR – complete remission; Cru – uncertain complete remission; PR – partial response; SD – stable disease; PD – progressive disease; OS – overall survival; EFS – event free survival; PFS – progression free survival; SE – standard error.

significantly lower among patients with DLBCL CS ≥ III in comparison to patients with DLBCL CS < III (70% ± 6 vs. 95% ± 2.8; $p = 0.0004$). Similar correlations were observed for EFS probability (55.4% ± 6 vs. 84.8% ± 4; $p = 0.0006$) and PFS probability (74.6% ± 8 vs. 97.9% ± 2; $p = 0.008$).

In contrast the presence of ≥2 extra nodal lesions and patients age > 60 years did not have negative prognostic impact on neither response to treatment nor survival. 108 (74%) patients with no or one extra nodal site of DLBCL experienced CR/CRu in comparison to 20 (62.5%) patients with two or more extra nodal lesions ($p = 0.2$). 54 (74%) patients >60 years old achieved CR or CRu in comparison to 74 (70.5%) of patients at the age of 60 or less ($p = 0.73$). OS probability for patients with ≥2 vs. <2 extra nodal sites was 78.5% ± 8 vs. 81.5% ± 4; $p = 0.39$ and OS probability for patients >60 vs. <60 years old was 81.8% ± 7.5 vs. 79.9% ± 4.5; $p = 0.45$. Similar correlations were observed for EFS and PFS probabilities. Survival data are reported at 3 years of observation.

In a multivariate analysis the only independent negative prognostic factor for the chance of achieving CR/CRu was elevated LDH level (HR = 0.43, 95% CI, 0.21–0.89; $p = 0.002$). Independent negative prognostic factors for OS were stage of the disease III/IV (HR = 4.61, 95% CI, 1.32–16.1; $p = 0.02$) and elevated LDH level (HR = 3.12, 95% CI, 1.3–7.47; $p = 0.01$). Disease stage III/IV was the only independent negative prognostic factor for PFS (HR = 10.21, 95% CI, 1.23–85.1; $p = 0.03$) and EFS (HR = 2.29, 95% CI, 1.11–4.71; $p = 0.02$). Multivariate analysis of CR/CRu, OS, EFS and PFS in relation to IPI components is presented in Table IV.

Discussion

We evaluated the performance of IPI components in DLBCL patients treated with R-CHOP regimen to assess if immunochemotherapy influenced their prognostic value. IPI is a clinical prognostic model that predicts outcome [20]. Based on five independent prognostic factors it identifies four prognostic groups: low risk, low intermediate risk, high-intermediate risk and high risk with 5-years OS values 73%, 51%, 43% and 26%, respectively [20]. It is worth to note, however, that IPI was designed before introducing rituximab to standard treatment of DLBCL patients. In the rituximab era a revised IPI (R-IPI), redistributing the five IPI components into three prognostic groups (very good, good and poor) was designed, but it does not identify the group of patients whose 4-year OS probability is lower than 50% [21]. This group will probably require more intensive treatment immediately after DLBCL diagnosis [3].

New molecular prognostic markers were identified, but none of them gain wide practical acceptance. According to gene expression profiling we distinguish germinal center

Table IV – Multivariate analysis of CR/CRu, OS, EFS and PFS in relation to IPI components
Tabela IV – Analiza wielowariantowa zależności od poszczególnych składowych IPI szansy uzyskania CR/CRu, OS, EFS i PFS

Variables	CR/CRu			OS			EFS			PFS		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
CS ≥ III	0.47	(0.21–1.0)	0.06	4.61	(1.32–16.1)	**0.02**	2.29	(1.11–4.71)	**0.02**	10.21	(1.23–85.1)	**0.03**
ECOG-PS ≥ 2	0.65	(0.28–1.48)	0.3	1.9	(0.83–4.35)	0.1	1.79	(0.96–3.3)	0.06	2.12	(0.51–8.76)	0.3
Age > 60	1.54	(0.74–3.21)	0.2	0.53	(0.23–1.25)	0.1	0.94	(0.53–1.67)	0.83	0.92	(0.23–3.63)	0.9
LDH > N	0.43	(0.21–0.89)	**0.002**	3.12	(1.3–7.47)	**0.01**	1.73	(0.95–3.13)	0.07	0.97	(0.25–3.76)	0.9
Extranodal lesions ≥ 2	0.71	(0.29–1.76)	0.5	1.34	(0.51–3.53)	0.55	1.2	(0.59–2.43)	0.6	0.33	(0.04–2.79)	0.3

HR – hazard ratio; CR – complete remission; CRu – uncertain complete remission; OS – overall survival; EFS – event free survival; PFS – progression free survival; ECOG-PS – Eastern Cooperative Oncology Group Performance Status; CS – clinical stage; LDH – lactate dehydrogenase. Variables were regarded as significant at a level of 0.05 and are shown in bold.

B-cell like DLBCL (GCB) and activated B-cell like DLBCL (ABC) [24–26]. In the rituximab era patients with GCB subtype gain significantly longer PFS and OS [27]. Gene expression profiling is still an expensive procedure and immunohistochemistry models, identifying GCB or non-GCB subtype, are not fully consistent with the real state [28]. To date diagnosis of GCB or non-GCB subtype should not influence treatment decision making [3]. The mechanism of *BCL-2* overexpression, *MYC* and *TP 53* dysfunction, MHC loss, some micro-RNA signatures, high Ki67 or type of tumor microenvironment are also supposed to be adverse prognostic factors, but without impact on treatment strategy [27, 29–35].

Extra nodal DLBCL accounts for 25–40% cases [1]. It is a heterogeneous entity, with various clinical course. The role of immunochemotherapy in treatment of patients with extra nodal DLBCL was lastly discussed, but data are sparse and controversial. The studies are retrospective in their nature and the largest analyses are based on Asian population [15–18]. It seems that adding rituximab to chemotherapy does not improve outcomes in patients with extra nodal DLBCL, at least among cases in early clinical stage [36, 37]. However, in rituximab era extra nodal involvement is no longer independent prognostic factor, so one could conclude, that immunochemotherapy improves outcomes in these patients. These observations might depend on DLBCL localization. Few retrospective studies identified localizations like pleura, peritoneum, esophagus, adrenals, pancreas, ovaries, uterus, testis, small intestine, bone marrow, which are associated with significantly worse prognosis, even when treated with rituximab [38, 39]. In contrast patients with DLBCL affecting Waldeyer's ring or stomach have better treatment outcomes [40, 41]. In our analysis the presence and number of extra nodal lesions were not prognostic in patients treated with R-CHOP regimen. Also the type of extra nodal localizations did not affect prognosis, but subgroups of patients were relatively small and heterogeneous. It is worth to note that in enhanced IPI (NCCN-IPI) extra nodal DLBCL is an independent negative prognostic factor, irrespective of the number of extra nodal localizations [42]. In aaIPI extra nodal involvement is not taken into account [20].

In our analysis the only independent negative prognostic factor for the chance of achieving CR/CRu was elevated LDH level. CS $\geq$ III was within statistical significance. Elevated LDH level and advanced stage of the disease were also negative prognostic factors for OS. On the basis of these results, it seems that in the rituximab era the ''volume'' of DLBCL is the most powerful prognostic marker. These observations are in accordance with available literature [17, 18, 43, 44].

Patient's age $>$ 60 was not an independent prognostic marker in our analysis. Some authors postulate changing the age cut-off point into 70 (elderly IPI, E-IPI) or 75 years (NCCN-IPI) [42, 45]. Further analyses of randomized trials like RIVOVER60 trial showed that patient's age $\geq$ 70 but not 60 is an adverse prognostic factor [13]. In these cases age-related co-morbidities play crucial role [46]. The presence of co-morbidities often does not allow conducting full-dose treatment and affects OS. It also has influence on patient's performance status, independent of DLBCL. On the other hand, even in patients >80 years without significant contraindications applying R-CHOP is safe and improves treatment outcomes [3]. R-miniCHOP, with reduced doses of cytostatic agents, is also worth considering [3, 36]. In elderly patients treatment decision making should be based not only on IPI or E-IPI but also on co-morbidity score and comprehensive geriatric assessment (CGA) [47].

It seems that in recent years the prognostic significance of poor performance status decreased. Poor PS is often caused by advanced DLBCL or its unfavorable localization. Immunochemotherapy, assisted by appropriate supportive care, could in short time lead to marked improvement. Even if poor performance status results from co-morbidities, additional treatment can allow an optimal DLBCL therapy. In such cases, however, the risk of death is higher and independent of DLBCL progression.

Our study is retrospective in nature, with the consequent limitations, like potential interpretative errors resulting from different conditions during treatment of individual patients. The weak point of this analysis is also relatively small group of patients, especially in subgroups with different extra nodal localizations. On the other hand, extra nodal DLBCL is relatively rare and very heterogeneous disease entity, so conducting statistically powerful study with such group of patients is difficult. Further, multicenter studies are needed to determine applicability of our observations for different DLBCL localizations.

In conclusion, neither presence of extra nodal involvement, nor the type of DLBCL localization has a prognostic impact in the rituximab era. Among DLBCL patients receiving R-CHOP regimen elevated LDH level and clinical stage III/IV were independent negative prognostic factors, in contrast to performance status and patient's age. These observations should be verified in studies on independent patient's populations, preferably prospective clinical trials.

Authors' contributions/Wkład autorów

A.B.-R. – study design, data collection and interpretation, statistical analysis, manuscript preparation, and literature search. S.G. – study design, data interpretation, statistical analysis, and manuscript preparation. E.N. – study design. M.S. – data collection and literature search. E.C. – data collection.

Conflict of interest/Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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