ORIGINAL ARTICLE

# Role of rituximab in the first-line therapy of high-risk diffuse large B-cell lymphoma: a retrospective analysis by the Polish Lymphoma Research Group

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**KEY WORDS**

CHOP protocol, diffuse large B-cell lymphoma, immunochemotherapy, International Prognostic Index, rituximab

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**ABSTRACT**

**INTRODUCTION** R-CHOP immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) is a standard first-line treatment for diffuse large B-cell lymphoma (DLBCL). None of the randomized trials have proved a statistically significant overall survival (OS) benefit in high-risk subgroups according to the International Prognostic Index (IPI).

**OBJECTIVES** We retrospectively investigated the role of adding rituximab to anthracycline-based chemotherapy in patients with high-risk DLBCL according to the IPI.

**PATIENTS AND METHODS** A total of 371 patients with high-risk DLBCL treated at 15 Polish hematology centers were retrospectively analyzed in 2 distinct age groups: older than 60 years and 60 years old or younger. Response rates, OS, and progression-free survival (PFS) were compared and analyzed.

**RESULTS** The overall response rate (ORR) of high-risk DLBCL patients significantly improved in rituximab-treated patients compared with patients treated without rituximab (76.7% vs 95.6%; $P < 0.05$). The R-CHOP immunochemotherapy prolonged survival in both older and younger subgroups. The 5-year projected OS and PFS in younger patients treated with rituximab vs chemotherapy alone were 42% vs 38% and 46% vs 27%, respectively ($P < 0.05$), while the 5-year projected OS and PFS in older patients treated with rituximab vs chemotherapy alone were 82% vs 52% and 67% vs 45%, respectively ($P < 0.05$).

**CONCLUSIONS** With all the limitations of a retrospective analysis, the superiority of adding rituximab to CHOP combination chemotherapy has been clearly demonstrated regarding ORR, OS, and PFS in both age subgroups of patients with high-risk DLBCL.

**INTRODUCTION** Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive non-Hodgkin lymphoma (NHL), with survival without treatment measured in months. The most frequently used combination chemotherapy regimen, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), was introduced in 1973 by the National Cancer Institute group (George Canellos, Bruce Chabner, Phillip Schein, Vincent DeVita, and Robert Young). Its efficacy was

**TABLE 1** Characteristics of patients with diffuse large B-cell lymphoma (age, >60 y)

| Parameter | | CHOP n = 25 | R-CHOP n = 150 | *P* value |
|---|---|---|---|---|
| age, y | | 71 (61–83) | 70 (61–90) | NS |
| sex | male | 13 (52) | 83 (55.3) | NS |
| | female | 12 (48) | 67 (44.7) | |
| ECOG performance status | 0–1 | 19 (76) | 113 (75) | NS |
| | > 1 | 6 (24) | 27 (25) | |
| Ann Arbor clinical stage | I–II | 4 (16) | 8 (6) | <0.05 |
| | III–IV | 21 (84) | 142 (94) | |
| presence of B symptoms | | 17 (68) | 106 (71) | NS |
| no. of extranodal sites | 0–1 | 5 (20) | 81 (54) | <0.05 |
| | >1 | 20 (80) | 69 (46) | |
| bulky tumor ≥7cm | | 8 (32) | 29 (19) | NS |
| bone marrow involvement | | 5 (20) | 12 (8) | NS |
| elevated LDH levels | | 18 (72) | 98 (65) | NS |
| IPI score | 3 | 13 (52) | 82 (55) | NS |
| | 4 | 8 (32) | 54 (36) | |
| | 5 | 4 (16) | 14 (9) | |

Data are presented as median (range) or number (percentage) of patients.

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NS, nonsignificant, R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

**TABLE 2** Characteristics of patients with diffuse large B-cell lymphoma (age, ≤60 y)

| Parameter | | CHOP n = 53 | R-CHOP n = 143 | *P* value |
|---|---|---|---|---|
| age, y | | 42 (18–60) | 47 (17–60) | NS |
| sex | male | 33 (62.2) | 78 (54.5) | NS |
| | female | 20 (37.8) | 65 (45.5) | |
| ECOG performance status | 0–1 | 31 (58) | 80 (55.9) | NS |
| | >1 | 22 (42) | 62 (44.1) | |
| Ann Arbor clinical stage | I–II | 3 (5,5) | 6 (4) | NS |
| | III–IV | 50 (94.5) | 137 (96) | |
| presence of B symptoms | | 45 (85) | 124 (87) | NS |
| no. of extranodal sites | 0–1 | 6 (11) | 23 (16) | NS |
| | >1 | 47 (89) | 120 (84) | |
| bulky tumor >7cm | | 14 (26) | 54 (38) | NS |
| bone marrow involvement | | 8 (15) | 21 (15) | NS |
| elevated LDH | | 53 (100) | 138 (97) | NS |
| IPI score | 3 | 35 (66) | 99 (69) | NS |
| | 4 | 18 (34) | 44 (31) | |

Data are presented as median (range) or number (percentage) of patients.

Abbreviations: see TABLE 1

proved in a prospective randomized phase III trial by the Southwest Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG). The CHOP protocol was less toxic than more intensive third-generation regimens and had comparable efficacy—a 3-year overall survival (OS) of about 50%.[1] Several further studies have demonstrated an increase in response rates by 10% to 20% and prolonged OS in patients with DLBCL by adding rituximab, a chimeric anti-CD20 monoclonal antibody, to CHOP chemotherapy.[2-8] Immunochemotherapy (rituximab CHOP: R-CHOP) is now regarded as the first-line standard of care for all patients with DLBCL regardless of age and the International Prognostic Index (IPI). The IPI predicts the outcome of patients with NHL depending on the presence of 5 risk factors.[9] Its validity in the rituximab era has been confirmed.[10] However, most younger patients included in the above randomized trials had a low-risk disease according to the IPI, and none of the trials including elderly patients confirmed a statistically significant improvement in OS in high-risk patients. We report the results of a retrospective analysis of high-risk patients with DLBCL of both age groups (older and younger), which compared the outcome of patients receiving rituximab-based regimens or chemotherapy alone.

## PATIENTS AND METHODS

We retrospectively reviewed the files of 371 adult patients with newly diagnosed DLBCL treated at 15 Polish hematology centers (associated by the Polish Lymphoma Research Group) between 2004 and 2012. The inclusion criteria were as follows: newly diagnosed DLBCL according to the World Health Organization's classification; age >18 years; IPI score, 3–5 (high-intermediate and high risk); CHOP-like chemotherapy; and curative intent of treatment.

Patients were classified into age subgroups (175 patients were aged more than 60 years and 196 patients—60 years or younger). In the older subgroup, 150 patients were treated with R-CHOP and 25—with CHOP. In the younger subgroup, 143 patients were treated with R-CHOP and 53—with CHOP. CHOP-treated patients were matched for their characteristics to R-CHOP-treated patients (TABLES 1 and 2). Patients were treated without rituximab during the years from 2004 to 2007 and with rituximab during the years from 2004 to 2012. Supportive care during treatment was administered according to standard clinical practice. Patients with specific risk factors (such as paranasal sinus, testicular, epidural, or bone marrow involvement, involvement of 2 or more extranodal sites, or elevated lactate dehydrogenase [LDH] levels) were given central nervous system prophylaxis with intrathecal methotrexate and cytarabine or liposomal cytarabine.[11] The IPI, assessed before chemotherapy, was based on the presence of risk factors: age, >60 years; involvement of more than 1 extranodal sites; elevated LDH levels; Ann Arbor clinical stage, III or IV; and performance status according to the ECOG, 2–4. The risk groups according to the IPI were determined as high-intermediate risk with 3 risk factors present and high risk with 4 to 5 risk factors present.[9] The characteristics of the patients were similar between the study subgroups (TABLES 1 and 2). There were considerable differences between the subgroups in the distribution of

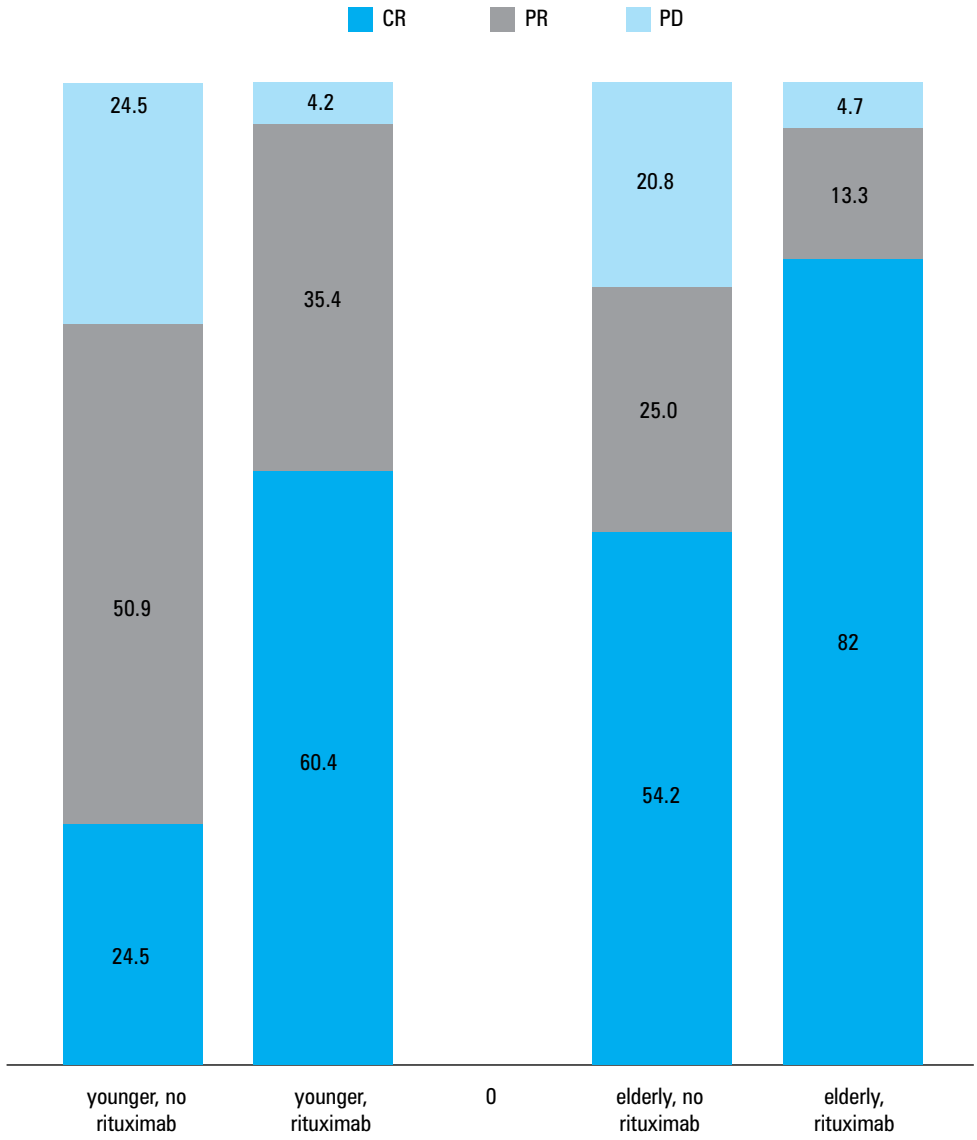


**FIGURE 1** Response rates (percentage) Abbreviations CR, complete response; PD, progressive disease; PR, partial response

risk factors. In the younger subgroup, compared with the older subgroup, a significantly higher percentage of patients had a performance status exceeding 1 (43% vs 24.6%; $P < 0.05$), extranodal involvement at more than 1 site (85.2% vs 50.8%; $P < 0.05$), LDH levels exceeding the reference range (97% vs 66.2%; $P < 0.05$), and bulky disease (34.6% vs 21%, $P < 0.05$).

Data on clinical outcome and other clinical parameters were obtained using specific questionnaires and entered into the database. Response rates, OS, and progression-free survival (PFS) were analyzed separately for the study subgroups, comparing the results of chemotherapy with or without rituximab.

The most common chemotherapy regimen was CHOP (89%): cyclophosphamide (750 mg/m$^2$), doxorubicin (50 mg/m$^2$), vincristine (1.4 mg/m$^2$), and prednisone (100 mg/d for 5 days). In 11% of the patients, CHOP-like regimens were usually administered with alternative anthracyclines: liposomal doxorubicin (R-COMP) and mitoxantrone (CN3OP) or the addition of bleomycin (CHOP-Bleo). Patients were scheduled to receive from 6 to 8 cycles of therapy. The median number of the administered cycles was 6.4 (range, 4–10). If rituximab was given, a standard dose of 375 mg/m$^2$ with each cycle of chemotherapy was administered. Radiation therapy was given to 24% of patients treated without rituximab and to 17% of patients treated with rituximab (in most cases, as the consolidation treatment of bulky disease). None of the patients were subjected to consolidation high-dose therapy with autologous stem cell support (ASCT) as part of the first-line regimen.

After the completion of therapy, the routine follow-up including imaging studies according to the standard protocol used in our center was started. Refractory and relapsed cases were treated with different salvage regimens, including ASCT, whenever applicable. The median follow-up period was 20.9 months (range, 1–171 months).

Clinical characteristics and outcome variables were compared between patients treated with and without rituximab in younger and older subgroups. Patient characteristics were compared between the groups using the $\chi^2$ test for categoric variables and the $t$ test or Mann–Whitney

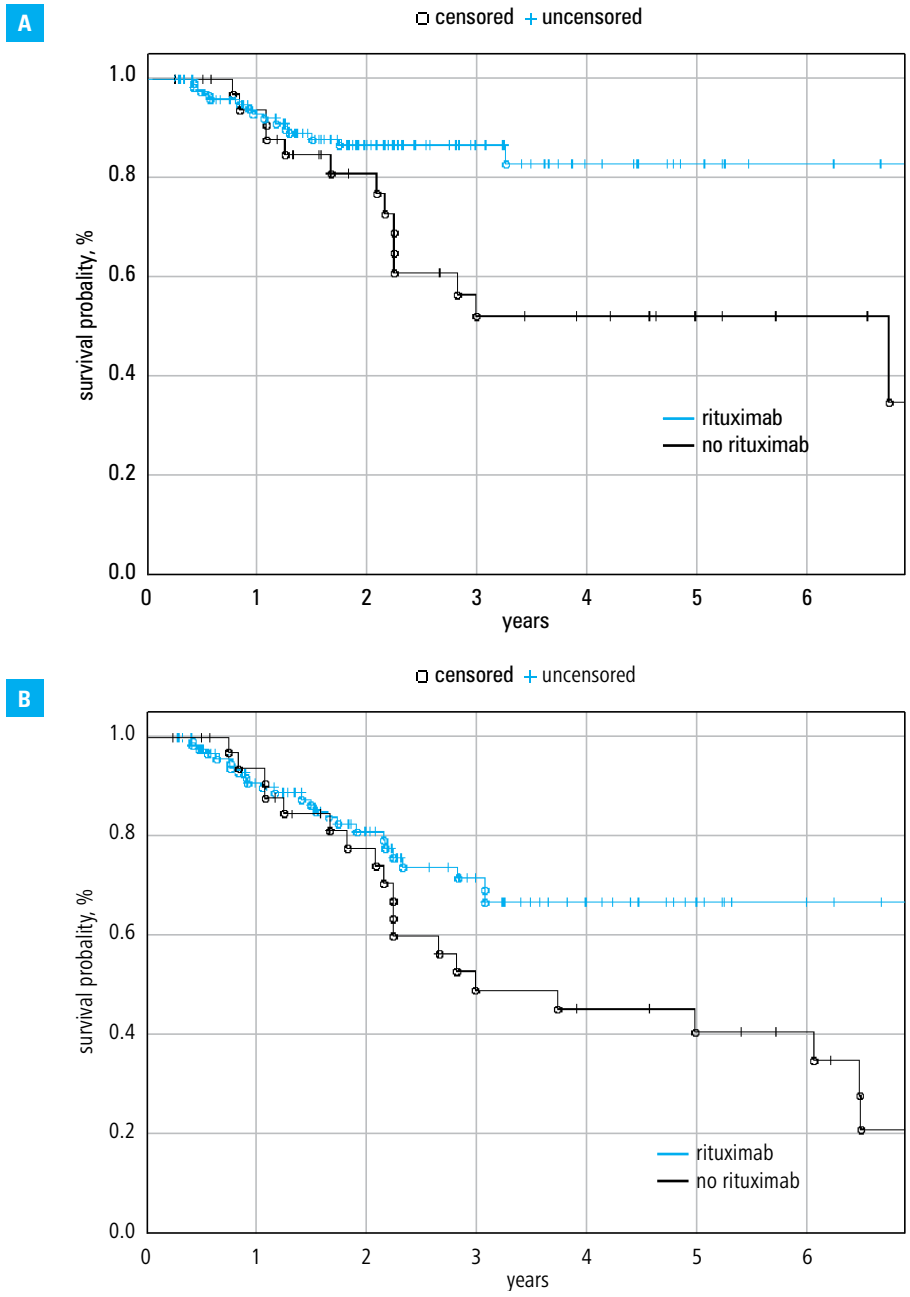


**FIGURE 2** Overall survival (**A**) and progression-free survival (**B**) in older patients

test for continuous variables. The main analyzed endpoints included PFS and OS. PFS was defined as the time from the date of diagnosis to disease progression, relapse, or the date the patient was last known to be alive. OS was measured from the date of diagnosis until death from any cause or the date of the last follow-up. PFS and OS were calculated using the Kaplan–Meier method and compared between the groups using the log-rank test. A *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the Statistica software version 10 (Statsoft, Kraków, Poland).

**RESULTS** A total of 371 high-risk (IPI, 3–5) patients were analyzed: 175 aged more than 60 years and 196 aged 60 years or younger. We analyzed differences between patients treated with and without rituximab separately for each age group. As previously described (**TABLES 1** and **2**), the groups were fully comparable and similar in terms of risk factors and other clinical details.

Using data from medical history, physical examination, and imaging studies, disease response to treatment was determined by the International Workshop Criteria.[12] Rituximab was shown to increase response rates both in younger and in elderly subgroups with high-risk DLBCL. The overall response rate (ORR) improved from 75.4% and 79.2% in the period before the use of rituximab to 95.8% and 95.3% during the use of rituximab in the younger and elderly subgroups, respectively (**FIGURE 1**). In particular, the introduction of rituximab improved the rate of complete response: from 24.5% to 60.4% in younger patients and from 54.2% to 82.0% in older patients. The incidence of progressive disease decreased from 24.5% to 4.2% and 20.8% to 4.7% in younger and older patients, respectively.

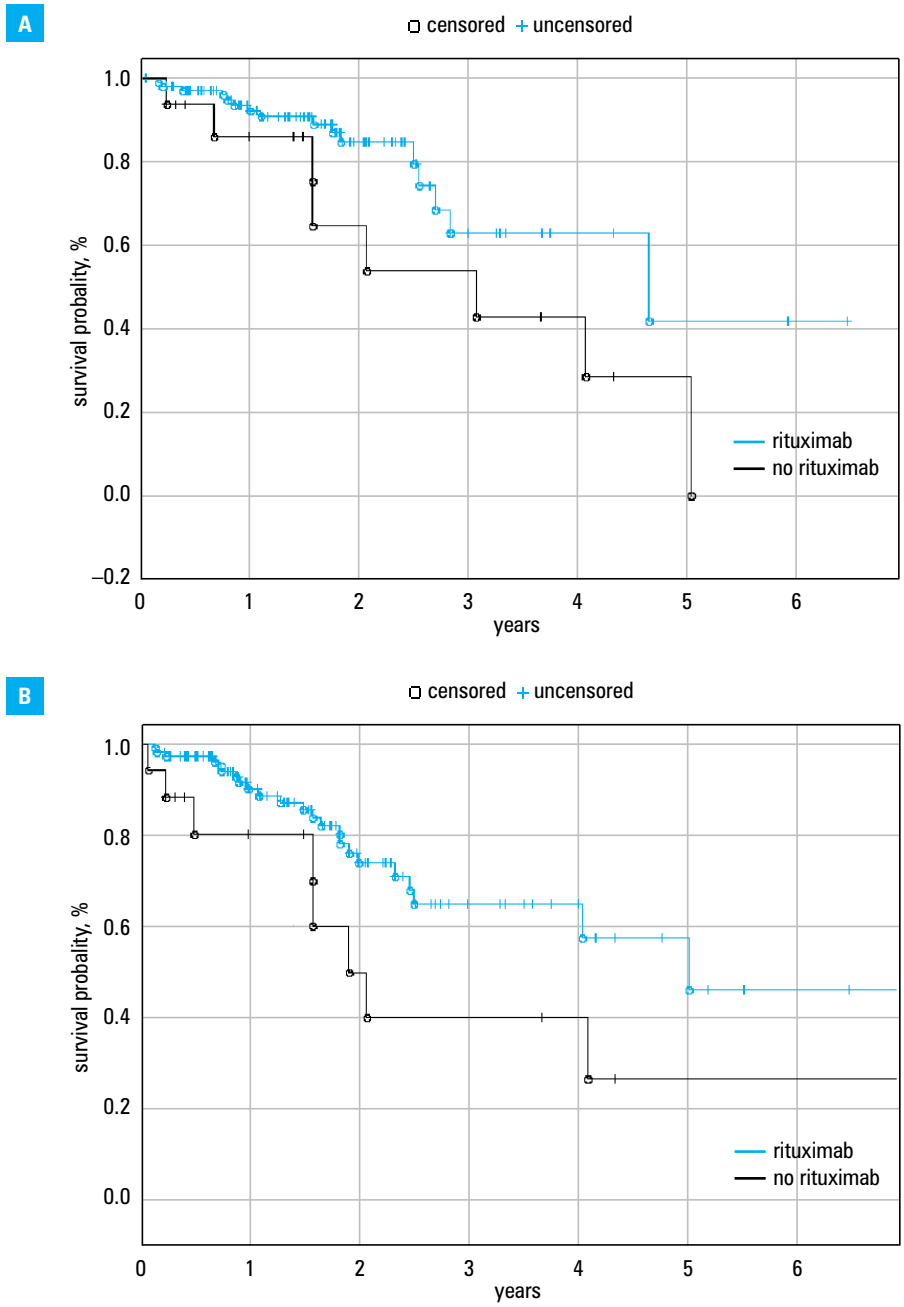


**FIGURE 3** Overall survival (**A**) and progression-free survival (**B**) of younger patients

The projected 5-year OS was significantly better in the group treated with rituximab compared with that treated with chemotherapy alone: 82% vs 52% ($P$ <0.05) for older patients and 42% vs 38% ($P$ = 0.05) for younger patients (FIGURES 2 and 3). Moreover, the addition of rituximab to anthracycline-based chemotherapy significantly increased the projected 5-year PFS in both age groups: from 45% to 67% ($P$ = 0.05) in older patients and from 27% to 46% ($P$ = 0.05) in younger patients. We showed the superiority of rituximab-based treatment in patients with high-risk and high-intermediate-risk DLBCL independently of age.

**DISCUSSION** It is generally accepted that immunochemotherapy (R-CHOP) in patients with DLBCL increases the ORR and prolongs both the PFS and OS, with almost no increase in toxicity. However, none of the prospective randomized trials demonstrated a clear benefit in high-risk disease, according to the IPI (TABLE 3). Two of those trials, evaluating the outcome of elderly patients, included high- and low-risk cases. Although all response assessment parameters (ORR, PFS, and OS) were significantly better in the entire group, prolonged OS was not observed in patients with an IPI score of 3 to 5. The only phase III trial with younger patients (<60 years)—MabThera International Trial (MInT)—included only low-risk DLBCL cases with an IPI score of 0 to 1.[7,8] Based on those studies, the R-CHOP regimen administered every 21 days is recommended as the first--line treatment for all patients with DLBCL irrespective of age.

In the prerituximab era, the German High Grade Study Group (DSHNHL) performed randomized trials, the results of which were in favor of dose-intense chemotherapy: CHOP-14 (recycled every 14 days) in elderly patients and

**TABLE 3** Randomized trials comparing R-CHOP vs CHOP alone in patients with diffuse large B-cell lymphoma

| Study | N | Age, y | IPI | PFS/EFS | *P* value | OS | *P* value |
|---|---|---|---|---|---|---|---|
| Coiffier (LNH-98.5 trial)[3-5] | 399 | 60–80 | HR: 54% | 5 y: 54% vs 30% | 0.001 | 5 y: 58% vs 45% | 0.001 |
| | | | | LR: 69% vs 34% | 0.001 | LR: 80% vs 62% | 0.02 |
| | | | | HR: 47% vs 29% | 0.001 | HR: 48% vs 39% | NS |
| Habermann (ECOG/CALGB 9703 trial)[6] | 632 | >60 | HR: 61% | 3 y: 52% vs 39% | 0.003 | 3 y: 67% vs. 57% | NS |
| Pfreundschuh (MInT trial)[7,8] | 824 | 18–60 | LR: 100% | 3 y: 79% vs. 59% | 0.001 | 3 y: 93% vs 84% | 0.0001 |
| | | | | 6 y: 64 % vs 80% | 0.001 | 6 y: 90% vs 80% | 0.0004 |

Abbreviations: EFS, event-free survival; HR, high risk; LR, low risk; OS, overall survival; PFS, progression-free survival; R, rituximab; others, see **TABLE 1**

**TABLE 4** Other randomized studies in diffuse large B-cell lymphoma

| Age | Clinical trials | Low-risk IPI | High-risk IPI |
|---|---|---|---|
| younger patients (≤60 years) | · Verdonck;[13] HOVON trial: CHOP-14 vs CHOP-21 | X | X |
| | · Récher;[18] GELA trial: R-ACVBP vs R-CHOP | X | |
| | · Schmitz;[19] DSHNHL 2002–1 trial: R-CHOEP-14 vs R-MegaCHOEP | | X |
| | · Glass;[20] retrospective: R-MegaCHOEP vs MegaCHOEP | | X |
| older patients (>60 years) | · Pfreundschuh;[12] DSHNHL NHL-B2 trial: CHOP-21 vs CHOP-14 | X | X |
| | · Pfreundschuh;[15] RICOVER-60: CHOP-14 vs R-CHOP-14 | X | X |
| | · Delarue;[17] LNH03–6B trial: R-CHOP-14 vs R-CHOP-21 | X | X |

Abbreviations: ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; DSHNHL NHL-B2, German High-Grade Non-Hodgkin Lymphoma Study Group, non-Hodgkin Lymphoma-B2; GELA, Study Group of the Adult Lymphoma; HOVON, Dutch–Belgian Cooperative Trial Group for Hematology-Oncology; LNH03-6B, non-Hodgkin Lymphoma 03-6B; others, see **TABLES 1** and **3**

CHOEP-14 (regimen with additional etoposide) in patients younger than 60 years.[13-15] Although the results in patients older than 60 years seemed to be even better after adding rituximab (R-CHOP-14, Ricover-60 trial),[17] 2 direct phase III comparisons with R-CHOP-21 confirmed equal efficacy and lower toxicity of the regimen administered every 21 days.[17,18] A similar approach undertaken by the French Study Group of the Adult Lymphoma demonstrated the superiority of the R-ACVBP regimen (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), although the clear benefit was limited only to low--risk group patients, with an IPI of 1.[19] Dose escalation in high-risk cases (ie, DSHNHL 2002-1 trial which consisted of R-MegaCHOEP followed by the ASCT) did not show any benefits.[20-21] In **TABLE 4**, we listed various trials aimed to improve the outcome of DLBCL patients, depending on age and IPI.

Our study provided better results than expected, especially in older patients, which probably results from the selection of patients. We only analyzed patients who received more than 3 cycles of chemotherapy. We excluded patients with comorbidities and complications precluding continuing chemotherapy or those with heart disease precluding the use of anthracyclines. The results for another 153 patients with low-intermediate risk DLBCL (an IPI score of 2) treated in the centers of the Polish Lymphoma Research Group are in line with the results of randomized trials: they demonstrated significantly better survival (PFS and OS) in both older and younger subgroups of patients (unpublished data).

There were no significant differences in risk factors between the subgroups (comparing patients with and without rituximab), but it should be emphasized that patients treated without rituximab were treated mostly during the years from 2004 to 2007; therefore, improvement in the OS may in part be related to better standards of supportive care. However, significant differences in PFS reflecting a relapse rate suggest a key role of the addition of rituximab.

The IPI has been used to assess prognosis for over 30 years. Better OS and PFS in older patients in our study may be associated with a less significant role of age as a risk factor in the era of more effective supportive care. On the other hand, younger patients had to have more disease-related risk factors to achieve an IPI score of 3 or 4. Most events occurred in the first 3 years after diagnosis, and relapse-free survival in the first 3 years was a favorable prognostic factor in both groups.

In conclusion, our findings demonstrate that the addition of rituximab to CHOP chemotherapy significantly improves the outcome of patients with high-risk DLBCL, given the ORR and PFS. Because our study had a retrospective design, it had a lower level of evidence than a prospective trial would have. However, so far, there have been no prospective trials comparing R-CHOP with

CHOP in young high-risk patients with DLBCL, and such studies are highly unlikely. Our results emphasize the need for developing new approaches to improve the outcome of young high-risk patients with DLBCL.

R-CHOP remains the standard of treatment. The intensification of doses in R-CHOP (dose-intense regimens) or its more frequent administration (dose-dense regimens) do not show improvement in the outcomes of treatment. The improvement of unsatisfactory results may depend on the addition of drugs with alternative mechanisms of action, such as lenalidomide, ibrutinib in the activated B-cell-like subtype, new monoclonal antibodies (anti-CD19, anti-CD38), or selective inhibitor of nuclear export, selinexor (KPT- 330), in patients with the germinal center B-cell-like subtype.[22-24]

**Contribution statement** WJ conceived the idea of the study. All authors were involved in study design and data collection. WJ and BO analyzed and interpreted the data, and performed the final revision. All authors approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

# Rola rytuksymabu w leczeniu pierwszego rzutu chłoniaka rozlanego z dużych komórek B dużego ryzyka – analiza retrospektywna Polskiej Grupy Badawczej Chłoniaków

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**SŁOWA KLUCZOWE**

chłoniak rozlany z dużych komórek B, immunochemioterapia, Międzynarodowy Wskaźnik Prognostyczny, protokół CHOP, rytuksymab

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**STRESZCZENIE**

**WPROWADZENIE** Immunochemioterapia R-CHOP (rytuksymab, cyklofosfamid, doksorubicyna, winkrystyna, prednizon) jest standardem leczenia pierwszego rzutu w przypadku chłoniaka rozlanego z dużych komórek B (*diffuse large B-cell lymphoma* – DLBCL). Żadne z badań randomizowanych nie udowodniło istotnej statystycznie korzyści w zakresie całkowitego przeżycia (*overall survival* – OS) w podgrupie dużego ryzyka wg Międzynarodowego Wskaźnika Prognostycznego (International Prognostic Index, IPI).

**CELE** Zbadaliśmy retrospektywnie rolę dodania rytuksymabu do chemioterapii opartej na antracyklinie u chorych z DLBCL dużego ryzyka wg IPI.

**PACJENCI I METODY** 371 chorych z DLBCL dużego ryzyka leczonych w 15 polskich ośrodkach hematologicznych poddano retrospektywnie analizie w dwóch odrębnych grupach wiekowych: >60 i ≤60 rż. Porównywano i analizowano odsetki odpowiedzi na leczenie, OS i przeżycie wolne od progresji (*progression-free survival* – PFS).

**WYNIKI** Całkowity odsetek odpowiedzi (*overall response rate* – ORR) u chorych z DLBCL dużego ryzyka istotnie zwiększył się u chorych leczonych rytuksymabem w porównaniu z chorymi leczonymi bez rytuksymabu (76,7% *vs* 95,6%; p <0,05). Immunochemioterapia R-CHOP wydłużyła przeżycie zarówno w młodszej, jak i starszej podgrupie chorych. 5-letnie rzutowane OS i PFS młodszych chorych leczonych rytuksymabem *vs* samą chemioterapią wynosiły odpowiednio: 42% *vs* 38% i 46% *vs* 27% (p <0,05), natomiast 5-letnie rzutowane OS i PFS starszych chorych leczonych rytuksymabem *vs* samą chemioterapią wynosiły odpowiednio: 82% *vs* 52% i 67% *vs* 45% (p <0,05).

**WNIOSKI** Z uwzględnieniem wszystkich ograniczeń analizy retrospektywnej, przewaga dodania rytuksymabu do chemioterapii skojarzonej CHOP została wyraźnie wykazana odnośnie do ORR, OS i PFS w obu podgrupach wiekowych pacjentów z DLBCL dużego ryzyka.