

Biosimilar Rituximab (Redditux) Added to CHOP Chemotherapy for De Novo Diffuse Large B-Cell Lymphoma Patients: Real-Life Single-Center Experience

Biyobenzer Rituksimab (Redditux) ile CHOP Kemoterapisinin Yeni Tanı Diffüz Büyük B-Hücreli Lenfoma Hastalarında Kullanımı: Gerçek Yaşam Tek Merkez Deneyimi

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Abstract

Objective: Redditux® (RED), as a biosimilar rituximab, was approved in Turkey for all indications of the original Mabthera® (MAB) in March 2018. The aim of our study was to evaluate the efficacy and safety of RED in de novo diffuse large B-cell lymphoma.

Materials and Methods: Fifty-one patients received RED combined with the CHOP regimen. The median follow-up was 31 months. The historical control group included 219 patients treated with the MAB-CHOP regimen and the median follow-up time was 38 months. We compared the response rates and survival outcomes of these RED-CHOP and MAB-CHOP cohorts.

Results: In the RED cohort, the overall response rate (ORR) at the end of the treatment protocol was 86%, with 37 (72.5%) cases of complete response (CR) and 7 (13.5%) cases of partial response (PR). In the historical MAB cohort, the ORR was 84%, with CR and PR rates of 82% and 2%, respectively. The 24-month progression-free survival (PFS) rates were 73.76% (95% confidence interval [CI]: 0.59-0.84) and 85.2% (95% CI: 0.79-0.90) for the RED and MAB cohorts, respectively (p=0.0106). The 24-month overall survival rates were 78.4% (95% CI: 0.64-0.87) and 81.4% (95% CI: 0.75-0.86) for the RED and MAB cohorts, respectively (p=0.7461). For patients with high revised International Prognostic Index scores, 24-month PFS was 45.5% (95% CI: 0.17-0.71) and 63% (95% CI: 0.37-0.80) for the RED and MAB cohorts, respectively (p=0.0711). In the RED cohort, central nervous system (CNS) relapse was significantly increased compared to the MAB cohort (10% vs. 1.83%, p=0.004). Among the RED cohort, bone involvement at the time of diagnosis was a risk factor for CNS relapse

Öz

Amaç: Rituksimab biyobenzeri olan Redditux® (RED), ülkemizde Mart 2018'de orijinal Mabthera® (MAB) molekülünün tüm endikasyonlarında kullanılmak üzere onaylandı. Çalışmamızda, yeni tanı DBBHL hastalarında RED'in etkinliğini ve güvenilirliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Elli bir hasta RED ile birlikte CHOP tedavisi aldı. Ortanca takip süresi 31 aydı. Tarihsel kontrol grubunda, MAB-CHOP ile tedavi edilmiş 219 hasta mevcuttu ve ortanca takip süresi 38 aydı. RED ve MAB-CHOP ile tedavi edilmiş grupların tedavi sonuçlarını karşılaştırdık.

Bulgular: RED grubunda genel yanıt oranı (GYO) %86 iken, 37 hastada tam yanıt (TY) (%72,5) ve 7 hastada kısmi yanıt (KY) (%13,5) elde edildi. Tarihi MAB grubunda ise GYO %84 iken TY ve KY oranları sırasıyla %82 ve %2 idi. Yirmi dört aylık progresyonsuz sağkalım (PSK), RED ve MAB grupları için sırasıyla %73,76 (%95 güven aralığı [GA] 0,59-0,84) ve %85,2 (%95 GA: 0,79-0,90) olarak saptandı (p=0,0106). 24-aylık genel sağkalım (GSK) oranları ise RED ve MAB grupları için sırasıyla %78,4 (%95 GA: 0,64-0,87) ve %81,4 (%95 GA: 0,75-0,86) idi (p=0,7461). Yüksek R-IPI skoru olan hastalarda 24-aylık PSK, RED ve MAB kohortları için sırasıyla %45,5 (%95 GA: 0,17-0,71) ve %63 (%95 GA: 0,37-0,80) bulundu (p=0,0711). RED grubunda MSS nüksü riski MAB grubuna göre anlamlı derecede artmış bulundu (%10'a karşı %1,83; p=0,004). RED kohortunda, tanı sırasında kemik tutulumu olması, MSS nüksü için risk faktörü olarak tespit edildi (p=0,028). Takipte 13 hasta vefat etti. İlacın sonlanmasına neden olacak ciddi yan etki gözlenmedi.



Abstract

($p=0.028$). Thirteen patients died in follow-up. There were no serious adverse events causing the cessation of the drugs.

Conclusion: RED has an ORR similar to that of MAB. However, PFS rates were worse in the RED cohort. Additionally, CNS relapse ratio was a major concern for our RED cohort. Large prospective controlled studies and real-life data with longer follow-up are needed to document the non-inferiority of RED compared to MAB.

Keywords: Rituximab, Biosimilar, Redditux, Diffuse large B-cell lymphoma, Non-Hodgkin lymphoma

Öz

Sonuç: RED, orijinal MAB molekülüne benzer GYO gösterdi. Ancak RED grubunda, MAB grubuna göre PSK oranları daha kötüydü. Ayrıca RED kohortumuzda MSS nüksü önemli bir sorundu. RED'in MAB'a eşdeğer etkinliğini ve güvenilirliğini doğrulamak için yüksek katımlı prospektif kontrollü çalışmalar, uzun takipli gerçek yaşam verilerine ihtiyaç vardır.

Anahtar Sözcükler: Rituksimab, Biyobenzer, Redditux, Diffüz büyük B-hücreli lenfoma, Non-Hodgkin lenfoma

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphomas (NHLs). Introduction of the biological product rituximab, a chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody, to B-cell NHL treatment significantly improved the response rates in cases of DLBCL [1]. Biosimilars are highly similar to reference biological products in terms of purity, potency, and safety [2]. Although they are identical to their reference products at the level of amino acid sequences, biosimilars have some differences at the protein level [3].

Redditux® (RED), a biosimilar rituximab first approved in India in 2007 [4], was approved in Turkey for all indications of the reference molecule Mabthera® (MAB) in March 2018. There are scarce relevant clinical trials and real-life experiences with hematological malignancies, including DLBCL. Since 2019, our hospital's administration decided to use the more affordable biosimilar RED due to its cost advantage after receiving approval from the Ministry of Health and being reimbursed.

Here we present data on our real-life experience with the biosimilar rituximab RED in cases of de novo DLBCL. We previously published our preliminary results [5]. The aim of the current analysis is to document the efficacy and safety of RED in de novo DLBCL by comparing it with a historical DLBCL cohort [6] treated with a MAB-based regimen.

Materials and Methods

All of the patients were diagnosed with de novo DLBCL using the criteria of the World Health Organization [7]. Cells of origin were determined according to the Hans protocol [8]. Bone marrow biopsy was conducted for all patients at the time of diagnosis. Staging and response assessment were performed using positron emission tomography/computed tomography (PET/CT) imaging. The Ann Arbor classification was used to stage the disease [9]. Tumor mass size of greater than 10 cm in diameter was defined

as bulky disease [10]. Patients with central nervous system (CNS) involvement were not included in the study. Complete response (CR), partial response (PR), progression, refractory disease, and relapse were defined according to Eastern Cooperative Oncology Group (ECOG) criteria for the MAB cohort [11] and according to the Lugano classification for the RED cohort [12].

All patients were treated at the same institution with the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) administered every three weeks and RED was used as rituximab (RED-CHOP). The treatment algorithm was designed according to the guidelines of the European Society for Medical Oncology [13]. CNS prophylaxis was administered as intrathecal methotrexate (IT-MTX) for patients with high CNS-International Prognostic Index (IPI) scores of ≥ 4 [14].

Results regarding efficacy and safety were compared with a cohort in which the patients had received rituximab in the form of the MAB-CHOP regimen. Those data were collected electronically with the permission of the İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty's hematology team.

Continuous variables were presented as medians and categorical variables were presented as numbers. Differences between groups were analyzed with chi-square tests. Both overall survival (OS) and progression-free survival (PFS) were censored at the last date for which information was available. The median duration of response, PFS rates, and OS rates along with their two-sided 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method. Survival functions were compared using the log-rank test. We also performed nearest neighbor matching analysis to match our RED and MAB cases.

Our study was approved by the İstanbul University, İstanbul Medical Faculty's Ethics Committee (2019/1454) and conducted in accordance with rules of good clinical practice and the Declaration of Helsinki. Statistical analyses were performed with STATA MP 17.

Results

General Characteristics

Between February and September 2019, a total of 51 DLBCL patients received the RED-CHOP regimen in the İstanbul Medical Faculty. The median age of these patients was 60 (range: 17-79) years and 57% of the cohort was male. Half of the patients were in the germinal center B-cell (GCB) subgroup. Twenty-eight patients (55%) had advanced stage (III-IV) disease. Bone marrow involvement was observed in 9 cases (17.7%). The revised IPI (R-IPI) score was low in 8 cases, whereas it was intermediate and high in 22 and 18 cases, respectively (Table 1).

The historical control group included 219 patients treated with the MAB-CHOP regimen. Almost half of these patients were male. One-third of the patients had disease of GCB origin and another third of non-GCB origin. The ratio of patients with unknown cells of origin was higher compared to the study cohort. Fifty-two percent of the historical cohort had advanced stage disease and 16.6% had bone marrow involvement at the initial presentation. The R-IPI score was high for 33.3% of these patients (Table 1).

Response Rates

A median of 6 cycles of the biosimilar (range: 4-8) were administered. Four patients' CNS-IPI scores were high and they

Table 1. Patient characteristics.

| | Redditux group (n=51) | Mabthera group (n=219) | p |
|----------------------------------|-----------------------|------------------------|-------|
| Median follow-up, months (range) | 31 (8-39) | 38 (1-106) | 0.002 |
| Median age, years (range) | 60 (17-79) | 55 (19-83) | 0.498 |
| Sex n, (%) | | | |
| Male | 29 (57) | 113 (52) | 0.498 |
| Female | 22 (43) | 106 (48) | |
| Subgroup n, (%) | | | |
| GCB | 25 (49) | 73 (33) | 0.097 |
| Non-GCB | 13 (25) | 71 (32) | |
| TCRBCL | 3 (6) | 0 | |
| NA | 10 (20) | 75 (35) | |
| Advanced stage n, (%) | 28 (55) | 114 (52) | 0.714 |
| Elevated LDH n, (%) | 23 (48) | 110 (50.5) | 0.750 |
| Extranodal sites >1 n, (%) | 14 (27.5) | 63 (28.8) | 0.851 |
| Age >60 years n, (%) | 26 (51) | 84 (38.4) | 0.098 |
| ECOG >1 n, (%) | 15 (29.4) | 30 (13.7) | 0.007 |
| Bulk >10 cm n, (%) | 8 (16) | NA | |
| Primary extranodal n, (%) | 12 (23.5) | 56 (25.6) | 0.762 |
| Bone involvement n, (%) | 11 (21.6) | NA | |
| Bone marrow involvement n, (%) | 9 (17.7) | 36 (16.6) | 0.856 |
| Liver involvement n, (%) | 4 (7.8) | 20 (9.2) | 0.764 |
| Stage n, (%) | | | |
| I | 10 (19.6) | 61 (27.9) | 0.369 |
| II | 13 (25.5) | 44 (20) | |
| III | 11 (21.6) | 59 (27) | |
| IV | 17 (33.3) | 55 (25.1) | |
| R-IPI score* n, (%) | | | |
| Low (0) | 8 (16.7) | 46 (21) | 0.753 |
| Intermediate (1-2) | 22 (45.8) | 100 (45.7) | |
| High (3-5) | 18 (37.5) | 73 (33.3) | |

*Available for 48 patients in the RED cohort.

GCB: Germinal center B-cell; TCRBCL: T-cell-rich B-cell lymphoma; NA: not available; LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; R-IPI: revised International Prognostic Index; RED: Redditux.

received IT-MTX injections as planned. Thirteen patients with bulky disease at diagnosis received involved field radiotherapy in addition to medical therapy [13]. In the RED cohort, the overall response rate (ORR) at the end of the treatment protocol was 86%, with 37 cases of CR (72.5%) and 7 cases of PR (13.5%). Seven patients had primary refractory disease. In the historical MAB cohort, the ORR was 84%, with CR and PR rates of 82% and 2%, respectively. Around 14% of patients were refractory in the RED cohort, whereas this value was 15.6% in the MAB cohort. The ORRs in patients with high R-IPI scores were 72.2% and 68.5% in the RED and MAB cohorts, respectively. The response rates of the RED and historical MAB cohorts are summarized in Table 2.

Survival Rates

The follow-up period was a median of 31 (range: 8-39) months and 38 (range: 1-106) months in the RED and MAB cohorts, respectively.

In the RED cohort, apart from 7 patients with primary refractory disease, 10 patients had progressive disease (PD) in follow-up. Median time to progression was 14.5 months for these 10 cases (range: 7-29 months).

The 24-month PFS rates were 73.76% (95% CI: 0.59-0.84) and 85.2 (95% CI: 0.79-0.90) for the entire RED and MAB cohorts, respectively. The log-rank test for equality of survivor functions favored MAB in PFS analysis (p=0.0106) (Figure 1A).

| | Redditux group (n=51) | Mabthera group (n=219) |
|---|----------------------------|---------------------------|
| Distribution of treatment responses (entire cohort) (%) | | |
| CR | 37 (72.6) | 178 (81.7) |
| PR | 7 (13.7) | 5 (2.3) |
| SD | 0 | 1 (0.5) |
| PD | 7 (13.7) | 34 (15.5) |
| Distribution of treatment responses among patients with high R-IPI scores of 3-5 (%) | | |
| CR | 8 (44.4) | 46 (63) |
| PR | 5 (27.8) | 4 (5.5) |
| SD | 1 (5.6) | 0 |
| PD | 4 (22.2) | 23 (31.5) |
| Survival rates | | |
| 24-month PFS | 73.76% (95% CI: 0.59-0.84) | 85.2 (95% CI: 0.79-0.90) |
| 24-month OS | 78.4% (95% CI: 0.64-0.87) | 81.4% (95% CI: 0.75-0.86) |

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; R-IPI: revised International Prognostic Index; PFS: progression-free survival; OS: overall survival; CI: confidence interval.

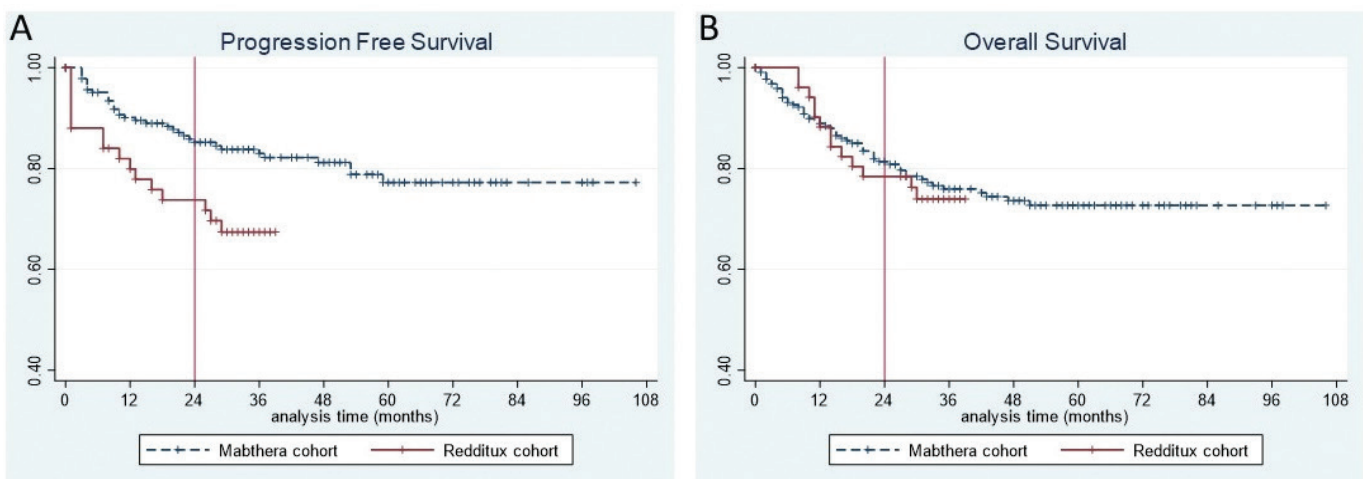


Figure 1. Survival curves according to treatment cohort.

The 24-month OS rates were 78.4% (95% CI: 0.64-0.87) and 81.4% (95% CI: 0.75-0.86) for the RED and MAB cohorts, respectively ($p=0.7461$) (Figure 1B). Thirteen patients died in the RED cohort.

Among subgroup analysis regarding patients with high R-IPi scores, the 24-month PFS was 45.5% (95% CI: 0.17-0.71) and 63% (95% CI: 0.37-0.80) for the RED and MAB cohorts, respectively ($p=0.0711$) (Figure 2A). The 24-month OS rates for the same groups were 46% (95% CI: 0.17-0.71) and 53% (95% CI: 0.34-0.69), respectively ($p=0.7461$) (Figure 2B).

Nearest Neighbor Matching Analysis

We also evaluated our results with nearest neighbor matching analysis to match RED and MAB cases for age (<60 vs. ≥60), gender, DLBCL cell type, disease stage (high vs. low), lactate dehydrogenase level (normal vs. high), performance score (ECOG 0-1-2 vs. 3-4), and number of extranodal sites (<2 vs. ≥2). The 24-month PFS rates for matched cases in the RED and MAB cohorts were 75.33% (95% CI: 0.58-0.86) and 88.99% (95% CI: 0.81-0.94), respectively ($p=0.0074$). The CNS relapse risk was also increased in the RED cohort among matched cases ($p=0.001$).

CNS Relapse

In the RED cohort, five patients (10%) experienced CNS relapse. Two of them had CNS-IPi scores of 1 and 3 at diagnosis, respectively; they did not receive prophylactic IT-MTX and had CNS involvement that developed during PD.

The remaining three patients achieved CR (n=2) or PR (n=1) at the end of the first-line treatment. The patients with CR had initial CNS-IPi scores of 0 and 2. Only one patient who had PR had a high CNS-IPi score of 5 at the time of diagnosis and received IT-MTX four times.

Of these 5 patients, 3 had bone involvement, defined as increased fluorodeoxyglucose uptake pointing to lymphoma involvement

in the bone tissue excluding the bone marrow at the time of diagnosis. When we evaluated the total cohort from the point of view of risk factors for CNS disease, we detected 3 of 11 cases with bone involvement entailing CNS disease, which was the only risk factor reflecting statistical significance ($p=0.028$).

Among the historical cohort that received the MAB-CHOP regimen, the CNS relapse rate was 1.83%, which was significantly lower compared to the RED cohort ($p=0.004$). Among the 25 patients with bone involvement, only one had CNS relapse ($p=0.389$).

Adverse Events and Deaths

Adverse events related to the RED-CHOP protocol were reported in 51% (n=26) of the cases (Table 3). However, these adverse events did not only include RED-related but also CHOP-related events. Dose modification was not needed for any patients in the RED cohort. The most common adverse event was neutropenia, which was seen in 39% of cases (n=20). Grade 2 infusion reactions (shivering, nausea, fever) requiring medical intervention were observed in 20% of these patients, accompanied by rash in half of the cases. Grades 3 and 4 adverse events were leukopenia (n=2; 4%), neutropenia (n=20; 39%), and febrile status in 2 cases, as well as anemia (n=6; 12%) and thrombocytopenia (n=3; 6%). There was no serious adverse event ending in the cessation of the drug. The safety results could not be compared to the historical MAB cohort due to missing data.

Thirteen patients died during follow-up. The causes of death were PD (n=8, two patients with CNS involvement), infection during allogeneic stem cell transplantation conditioning (n=1), post-COVID herpes zoster infection (n=1), COVID-related pulmonary disease (n=1), renal failure (n=1), and unknown (n=1).

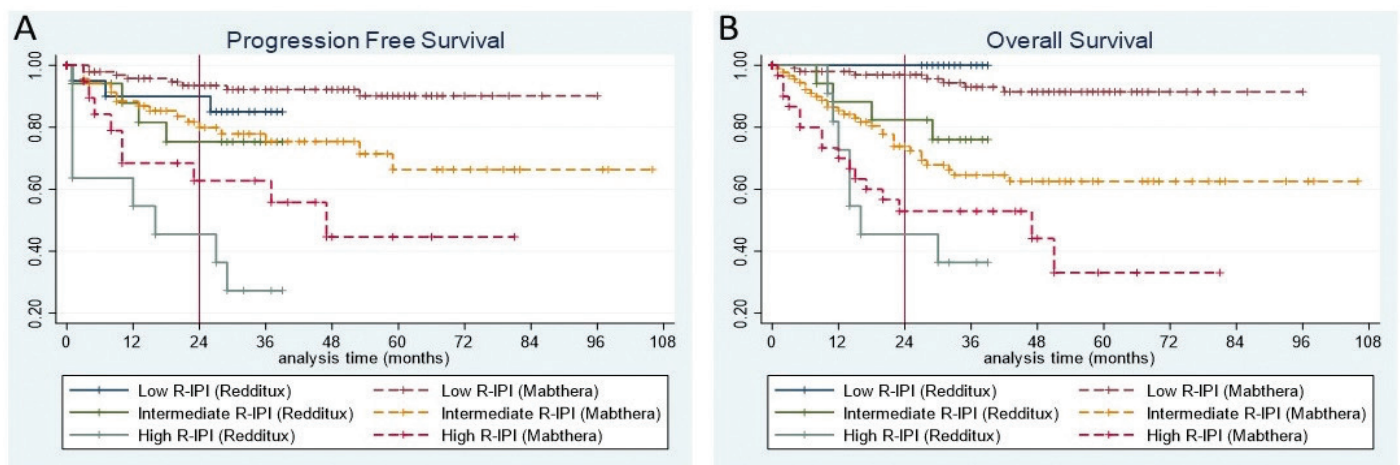


Figure 2. Survival curves according to treatment cohort and revised International Prognostic Index (R-IPi) scores.

Table 3. Adverse events in the Redditux cohort.

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---------|---------|---------|---------|
| Neutropenia | | | 9 | 11 |
| Infusion reactions requiring medical intervention | | 10 | | |
| Leukopenia | | | | 2 |
| Anemia | | 1 | 4 | 2 |
| Thrombocytopenia | 1 | 1 | 2 | |
| Peripheral neuropathy | 3 | | | |
| Fatigue | | 2 | 1 | |
| Neutropenic fever | 2 | | | |
| Pneumonia | | 2 | | |
| Urinary tract infection | | 2 | | |
| Loss of appetite | | 1 | | |
| Constipation | | 1 | | |
| Nausea | | 1 | | |
| Diarrhea | | 1 | | |
| Anal fissure | 1 | | | |
| Elevated transaminases | | 1 | | |
| Myalgia | | 1 | | |
| Bone pain | | 1 | | |

Discussion

Compared to reference molecules, biosimilars have minor differences on the protein level [3]. With the introduction of biosimilars, physicians gained more choice in the prescription process [15]. Roy et al. [4] compared RED, which was licensed in India as of 2007, with MAB in de novo DLBCL patients. Among a total of 223 patients, 101 received MAB and 72 received RED accompanied by a CHOP regimen. The ORRs were 89% and 95% for the original molecule and the biosimilar, respectively. Although the ORR was shown to be better in the RED group, the numbers of patients with advanced stage disease (44% vs. 56%), ECOG score of >1 (14% vs. 19%), bulky disease (24% vs. 31%), and high R-IPI score (15% vs. 23%) were less compared to the MAB cohort. The 5-year PFS and OS rates were 81% versus 72% and 76% versus 66% for the RED and MAB groups, respectively. There was no statistically significant difference in survival rates [4]. In the study published by Bankar et al. [16], the risk factors were more balanced between the RED and MAB cohorts [16]. The ORRs were 82.6% and 88.3% for RED and MAB, respectively.

The 5-year PFS and OS rates were also similar. DRL-rituximab, an FDA-approved rituximab biosimilar, was reported to have an ORR rate (82%; 95% CI: 0.70-0.90) comparable to that of MAB (84.8%; 95% CI: 0.73-0.92) in a cohort of 151 DLBCL patients [17]. There were no statistically significant differences in event-free survival, relapse, or progression and OS rates. Grade 3 and 4 adverse event rates were 72.3% and 84% in the DRL-rituximab and MAB groups, respectively. Among 13 patients who discontinued the study drug, eight of them were in the DRL-rituximab cohort and five were in the MAB cohort. The authors concluded that DRL-rituximab and MAB had comparable safety, efficacy, immunogenicity, and progression rates [17]. In a Dutch population-based study, Brink et al. [18] included 3553 and 876 patients receiving R-originator and R-biosimilar treatments, respectively. The authors reported similar ORR rates, being 85% versus 84% for the R-originator versus the R-biosimilar, respectively ($p=0.326$). Three-year OS rates among patients treated with original MAB compared to the rituximab biosimilar were 73% versus 73%, respectively. PFS rates were not reported in this study [18]. Other biosimilars such as RTX83 [19], HLX01 [20], Truxima [21], and IBI301 [22] had similar ORRs and safety profiles compared to MAB.

The ORR for RED-receiving patients was 86.3% in our cohort, with 37 cases of CR (72.5%) and 7 cases of PR (13.5%). One patient had SD whereas 6 patients had PD. Regarding the patients who had stage 2-4 disease, their ORRs were similar (85.3%). The 24-month estimated PFS was 73.76% and the OS was 78.4%. Compared to a historical trial [1], our CR rates among stage 2-4 patients seemed to be slightly lower (69% vs. 75%), although the ORRs were quite similar (86% vs. 82%).

Comparing our cohorts, the 24-month PFS rates were 73.76% (95% CI: 0.59-0.84) and 85.2% (95% CI: 0.79-0.90) for the RED and MAB cohorts, respectively. The log-rank test for equality of survivor functions favored MAB in PFS analysis ($p=0.0106$). For patients with high R-IPI scores, the 24-month PFS was 45.5% (95% CI: 0.17-0.71) and 63% (95% CI: 0.37-0.80) for the RED and MAB cohorts, respectively ($p=0.0711$).

The characteristics of the RED and MAB cohorts were largely similar; the only difference was the ratio of low-performance patients being higher in the RED cohort. However, the R-IPI score distributions were similar, and we think that the higher percentage of low-performance cases cannot be responsible for this significant difference in PFS rates. There were more cases in the GCB subgroup in the RED cohort. This may be due to the relatively higher rate of patients with cases of undetermined cell origin in the MAB cohort. PET/CT was widely used in response evaluation for the RED cohort, which may have contributed to the difference in PFS rates between the RED cohort and historical MAB cohort. It may be speculated that COVID-19-related deaths might have contributed to this difference; however, these two

particular cases did not affect the statistical significance of the difference between PFS rates. The population pharmacokinetics revealed that the volume of the central compartment was 0.95 L for the RED cohort, whereas it varied between 1.8 and 3.9 L for MAB [23]. Tout et al. [24] commented that this meant an estimated central volume of distribution of 68%-76% lower compared to MAB. Additionally, they calculated the elimination half-life of RED as 11.2 days, which varies between 20.2 and 100.5 days for MAB [24]. These pharmacokinetic differences may be the cause of PFS differences between our RED and MAB cohorts.

Compared to the CNS relapse rates ranging between 2% and 4% as reported in the literature [25,26,27], our finding was unexpectedly high in our cohort (10%). We administered IT-MTX for high-risk patients and recent data have shown that the CNS relapse risk is similar between patients receiving IT-MTX or high-dose methotrexate [28]. Among five patients who had CNS disease, only one had a high CNS-IPI score. Additionally, three of these five patients had initial bone involvement. From the point of view of bone involvement, three of eleven patients who had initial bone involvement had CNS relapse and this reached statistical significance ($p=0.028$). The CNS-IPI approach is relatively new and patient selection for CNS prophylaxis was not uniform in our historical MAB cohort. Similarly to the RED cohort, IT-MTX was used for patients with high risk of CNS relapse according to the physician's decision in the MAB cohort. Nevertheless, the CNS relapse rate was 1.83% in the historical MAB cohort, leading to a statistically significant difference ($p=0.004$).

Biosimilar rituximab was reported to affect the outcomes of DLBCL patients of low socioeconomic status who could not afford the original molecule in the study cohort, constituting an important financial advantage [29]. The main medicine cost of the R-CHOP regimen was shown to be due to rituximab in Europe and it was demonstrated that cost savings could be realized with the usage of biosimilar medications [30].

Retrospective evaluation and a low number of patients were the limitations of our study. We could not compare adverse events between the RED and MAB cohorts as the data were incomplete in the historical MAB cohort. It being licensed by the major European and US authorities would assure that physicians are globally more comfortable with the drug, but RED has not yet reached that stage.

Conclusion

According to our results, the biosimilar RED has similar OS rates in comparison to the original drug. However, compared to the historical MAB cohort, PFS rates were found to be worse in the RED group in the present study, and especially for the patients with high R-IPI scores. Additionally, the CNS relapse ratio was

a major concern for our cohort, and we could not analyze its relationship with the type of rituximab molecule. Head-to-head comparisons of RED and MAB pharmacokinetics, large prospective controlled studies, and more real-life data with longer follow-up periods are needed to document the non-inferiority and safety of RED compared to MAB.

Ethics

Ethics Committee Approval: Our study was approved by the İstanbul University, İstanbul Medical Faculty's Ethics Committee (2019/1454) and conducted in accordance with rules of good clinical practice and the Declaration of Helsinki.

Authorship Contributions

Design: S.K.B., M.Ö.; Data Collection or Processing: M.Ö., M.G.M., Ö.Ö., T.O.T., S.E., E.P.Ö., T.E., İ.Y.H., A.E.E., M.C.A., M.N.Y., T.S., M.N., B.F., A.YA., G.Y.; Writing: M.Ö., S.K.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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