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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

R-CHOP Chemotherapy with a Rituximab Biosimilar (Redditux®) for Patients with *de novo* Diffuse Large B-cell Lymphoma: First Preliminary Results of a Real-Life Single-Center Experience from Turkey

Biobenzer Rituksimab (Redditux®) İçeren R-CHOP Kemoterapisinin Yeni Tanı Diffüz Büyük B-hücreli Lenfoma Hastalarında Sonuçları: Türkiye'den Tek Merkez Gerçek Yaşam Verileri İlk Ön Sonuçları

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ABSTRACT

Objective: The introduction of rituximab significantly improved the response rates of patients with diffuse large B-cell lymphoma (DLBCL). The rituximab biosimilar Redditux® (RED) was approved in Turkey for all indications of the reference molecule MabThera® (MBT) in March 2018. The aim of this retrospective analysis was to evaluate the efficacy and safety of RED in de novo DLBCL.

Method: All patients diagnosed with DLBCL (n = 54) according to the World Health Organization criteria and followed up at the Hematology Division of İstanbul University, İstanbul Medical Faculty, from February 2019 to February 2020 were included in our analysis.

Results: Median age of the patients was 59 years (range: 17-79) and 57% of the patients were males. Median follow-up time was 10 months (range: 4-15). The overall response rate at the end of the treatment protocol was 86%, with 37 complete responses and 8 partial responses. The 12-month estimated overall survival was 76.8% [95% confidence interval (CI): 0.54-0.89] and the progression free survival was 78.5% (95% CI: 0.59 - 0.89). Adverse events were reported in 53% (n = 29) of the patients. The most common adverse event was grade 2 infusion reactions. There was no serious adverse event that instigated the cessation of the drug. Seven patients died during the follow-up due to central nervous system disease (n = 3), progressive disease (n = 2), and unknown causes (n = 2).

Conclusion: Compared to the initial historical trial of MBT, the complete response in stage 2, 3, and 4 patients seem to be slightly lower (69% vs. 75%), although the overall response rates are quite similar (86% vs. 82%). However, large prospective controlled studies and more real-life data with longer follow-up are needed to document the non-inferiority and safety of RED compared to MBT.

Keywords: Non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, rituximab biosimilar, redditux

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ÖZ

Amaç: Kimerik anti-CD20 insan immünoglobulin G1 monoklonal antikoru rituksimabın kullanıma girmesiyle B-hücreli lenfoproliferatif hastalıklarda yanıt oranları anlamlı derecede artmıştır. Biyobenzerler, Kabul edilmiş biyolojik moleküllere güvenirlik, saflık ve etki açısından yüksek oranda benzerlik gösteren biyolojik ürünlerdir. Biyobenzer Redditux® (RED), Mart 2018'de Türkiye'de, MabThera® (MBT) kullanılan tüm endikasyonlar için kullanım onayı aldı. Kurumumuzda, Şubat 2019'dan beri hematolojik hastalıklarda biyobenzer RED kullanıma girmiştir. Geriye dönük çalışmamızın amacı, yeni tanı DBBHL olgularında RED'in etkinliğini ve güvenirliğini değerlendirmektir.

Yöntem: DBBHL tanısı almış tüm hastalarda (n = 54) Dünya Sağlık Örgütü tanı kriterleri kullanılmış ve İstanbul Üniversitesi, İstanbul Tıp Fakültesi İç Hastalıkları Kliniği, Hematoloji Bölümü'nde, Şubat 2019 ile Şubat 2020 arasında tanı ve tedavi almışlardır.

Bulgular: Median yaş 59 (aralık: 17-79) olup olgularımızın %57'si erkektir. Ortalama takip süremiz 10 aydır (aralık: 4-15 ay). Tedavi protokolü sonunda genel yanıt oranı %86 olup, 37 hastada tam yanıt ve 8 hastada kısmi yanıt elde edilmiştir. Evre 2-4 olgularda genel yanıt oranı benzerdir (%86). On iki aylık genel sağkalım %76,8 [%95 güven aralığı (GA): 0,54 - 0,89] ve progresyonsuz sağkalım %78,5 (%95 GA: 0,59 - 0,89) olarak tespit edilmiştir.

Yan etkiler olguların %53'ünde tespit edilmiştir (n=29). En sık yan etki derece 2 infüzyon reaksiyonlarıdır. İlacın kesilmesini gerektiren herhangi bir ciddi yan etki gözlenmemiştir. Üç hasta merkezi sinir sistemi hastalığına, 2 hasta ilerleyici hastalığa ve 2 hasta tespit edilemeyen nedenlerle olmak üzere toplam 7 hasta kaybedilmiştir.

Sonuç: MBT'nin ilk orjinal makalesi ile karşılaştırdığımızda, evre 2-4 olgularda yanıt oranımız biraz düşük (%69 vs %75) olmakla birlikte genel yanıt oranlarımız (%86 vs %82) benzerdir. Geniş prospektif kontrollü çalışmalara ve uzun takip süreli daha fazla gerçek yaşam verisine, RED'nin MBT'ye benzer etki ve güvenirliği olduğunu gösterebilmek için ihtiyaç vardır.

Anahtar kelimeler: Non-hodgkin lenfoma, diffüz büyük B-hücreli lenfoma, biyobenzer rituksimab, redditux

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common morphological subtype of Non-Hodgkin's lymphoma (NHL), constituting about 40% of newly diagnosed NHLs. Due to its heterogeneous nature, it has variable clinical course and prognostic outcome.

The introduction of rituximab, a chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody, significantly improved the response rates in B-cell lymphoproliferative disorders [1]. Biosimilars are biologic products that are highly similar with accepted biological products in terms of safety, purity, and potency [2]. Over last years, they have attracted great attention worldwide as effective alternatives to biological agents. Biosimilar agents have differences on a protein level, although they are identical to the reference product on an amino acid sequence level [3]. The main aim of the production of biosimilars is to reduce the treatment costs, while increasing the prescription options of physicians [4].

The rituximab biosimilar Redditux® (RED) was approved in Turkey for all indications of the reference molecule MabThera® (MBT) in March 2018. Large clinical trials and real-life experiences are lacking in hematological malignancies, including DLBCL. Our institution decided to provide a rituximab biosimilar for hematological indications in February 2019 due to its efficacy and safety in the preliminary reports as well as its cost advantage. The aim of this retrospective analysis was to evaluate the efficacy and safety of RED in *de novo* DLBCL cohort.

METHOD

All patients (n = 54) diagnosed with DLBCL according to the World Health Organization criteria (5) and followed up at the Haematology Department of İstanbul University, İstanbul Medical Faculty, from February 2019 to February 2020 were included in this study.

This study was approved by İstanbul University İstanbul Medical Faculty ethical committee (2019/1454) and conducted in accordance with the rules of Good Clinical Practice and Helsinki Declaration.

Histopathological analysis of the lymph node materials was entirely performed in the Pathology Department of İstanbul Medical Faculty by an experienced haematopathologist. Bone marrow biopsy was applied to all patients at the diagnosis. Staging and response evaluation was done using positron emission tomography/computed tomography imaging. The staging of the disease was according to Ann Arbor classification [6]. Complete response (CR), partial response (PR), progression, refractory disease, and relapse were defined according to ECOG criteria [7]. Tumor mass with > 10 cm diameter was defined as "bulky disease" [8]. Almost all patients received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) regimen in three weekly cycles. Only one patient with primary central

nervous system (CNS) disease received MATRix regimen. The patients were primarily assessed according to their response to the first-line treatment. Both the response assessment and disease management was decided according to ESMO guidelines [9]. Statistical analyses were performed using STATA/SE version MP-64 for Windows.

RESULTS

General Characteristics

A total of 54 patients received RED combined with CHOP regimen. Median age was 59 years (range: 17-79) and 57% of the cohort was male. Half of the cases had germinal center B-cell subgroup. Thirty-one patients (57%) had advanced stage (III-IV) disease. Fourteen patients had extranodal involvement in more than one organ and eight patients had bulky disease. Bone marrow involvement was observed in 19% of the cohort. The international prognostic index (IPI) score was low in 8 patients, whereas it was intermediate and high in 24 and 19 patients, respectively (Table 1).

Treatment and Response Rates

Median follow-up time was 10 months (range: 4-15). Six patients had to switch from MBT to RED after a median of 2.5 cycles (range: 1-4). A median of six cycles of biosimilar (range: 4-8) was administered. All patients received CHOP based regimen, except one CNS lymphoma case who received four cycles of MATRix (high dose methotrexate, high dose cytarabine, and thiotepa) protocol. Three patients needed intrathecal prophylaxis and seven patients had additional radiotherapy for their initial bulky disease [9].

The overall response rate (ORR) at end of the treatment protocol was 86%, with 37 CR and 8 PR. Two patients had stable disease (SD) whereas 5 patients had progressive disease (PD). Regarding the patients who had stage 2 to 4 diseases, the ORR was similar (86%). The 12-month estimated overall survival (OS) was 76.8% [95% confidence interval (CI): 0.54 - 0.89] and progression free survival (PFS) was 78.5% (95% CI: 0.59 - 0.89) (Figure 1).

Adverse Events and Deaths

Adverse events (AE) were reported in 53% (n = 29) of the patients and the most common adverse event was grade 2 infusion reactions (shivering, nausea, fever), which required medical intervention (iv anti-histaminic, paracetamol, and dexamethasone) in 20% of the patients, accompanied with rash in half of them. Grade 3 and 4 AEs were leucopenia (n = 3; 5%), neutropenia (n = 22; 41%), fever, anemia (n = 6; 11%), and thrombocytopenia (n = 2; 4%). Grade 2 pneumonia

Table 1. Patient characteristics and treatment responses

	Patients who had to switch (n = 6)	**Redditux® only (n = 48)**	**All patients (n =54)**
Median age (range)	59 (48-72)	60 (17-79)	59 (17-79)
M/F	3 / 3 .	28 / 20 .	31 / 23
Subgroup			
GCB	4 (66%)	23 (48%)	27 (50%)
ABC	1 (17%)	12 (25%)	13 (24%)
TCRBCL	0	3 (6%)	3 (6%)
NA	1 (17%)	10 (21%)	11 (20%)
Advanced stage	4 (67%)	27 (56%)	31 (57%)
Elevated LDH (%)	3 (60%)	21 (46%)	24 (47%)
Extranodal site > 1 (%)	1 (17%)	13 (27%)	14 (26%)
Age > 60 (%)	3 (50%)	23 (49%)	26 (49%)
ECOG > 1 (%)	2 (33%)	14 (29%)	16 (30%)
Bulky > 10 cm (%)	2 (33%)	6 (13%)	8 (15%)
Primary extranodal (%)	1 (20%)	13 (30%)	14 (29%)
Bone marrow involvement	0	10 (21%)	10 (19%)
Liver involvement	1 (17%)	3 (6%)	4 (7%)
Stage			
I	1 (17%)	9 (19%)	10 (19%)
II	1 (17%)	11 (25%)	13 (24%)
III	2 (33%)	10 (21%)	12 (22%)
IV	2 (33%)	17 (35%)	19 (35%)
IPI score			
Good (0)	1 (20%)	7 (15%)	8 (16%)
Intermediate (1-2)	2 (40%)	22 (48%)	24 (47%)
High (3-5)	2 (40%)	17 (37%)	19 (37%)
Treatment			
Median doses of MabThera®	2.5 cycles		2.5 cycles
Median doses of Redditux®	5 cycles	6 cycles	6 cycles
Treatment respose (entire cohort)			
CR	4 (66%)	33 (72%)	37 (71%)
PR	0	8 (17%)	8 (15%)
SD	1 (17%)	1 (2%)	2 (4%)
PD	1 (17%)	4 (9%)	5 (10%)
Treatment respose (stage 2 - 4 disease)			
CR	3 (60%)	26 (70%)	29 (69%)
PR		7 (19%)	7 (17%)
SD	1 (20%)	1 (3%)	2 (5%)
PD	1 (20%)	3 (8%)	4 (9%)

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

and urinary tract infections were observed in four patients (7%). There was no serious adverse event that instigated the cessation of the drug.

Seven patients died during the follow-up due to CNS disease (n = 3), PD (n = 2), and unknown causes (n = 2). Among the three patients who died due to CNS disease, only one had primary CNS DLBCL. The other two patients had IPI scores of 3 and 4, respectively, at initial diagnosis and they both had primary refractory diseases.

DISCUSSION

The introduction of rituximab significantly improved the survival rates of patients with DLBCL, thereby becoming a milestone in the treatment of DLBCL [1]. Biosimilar agents have minor differences on a protein level compared to the reference products [3]. The main aim of biosimilar research is to reduce the treatments costs, while increasing the prescribing options of physicians [4]. RED, licensed in India since 2007, was compared with MBT in patients with DLBCL treated with three weekly R-CHOP [10]. In a total of 223 patients, 101 received MBT and 72 received RED. The ORR was 89% and 95% for the original molecule and the biosimilar one, respectively. Although the ORR was reported to be better in the biosimilar group, the number of patients with advanced stage disease (44% vs. 56%), ECOG score >1 (14% vs. 19%), bulky disease (24% vs. 31%), and high revised-IPI score (15% vs. 23%) were lesser compared to the original molecule cohort. The 5-year OS rates were 76% and 66%, while the PFS rates were 81% and 72% for the biosimilar and original molecule groups, respectively. The differences in the survival rates were not statistically significant [10]. In a newly published DLBCL cohort, the risk factors were more equilibrated between MBT and RED groups [11]. The ORR was 88.3% and 82.6% for the original molecule and rituximab biosimilar groups, respectively. The 5-year OS and PFS rates were similar between the two groups [11]. In another cohort of a total of 151 patients, another rituximab biosimilar, DRL-rituximab, was reported to have similar ORR rates (82%) compared to MBT (84.8%) and the authors concluded that the biosimilar and original molecule had comparable efficacy, safety, immunogenicity, and progression rates [12]. Other biosimilar also had similar ORR and safety profiles compared to MBT [13-15].

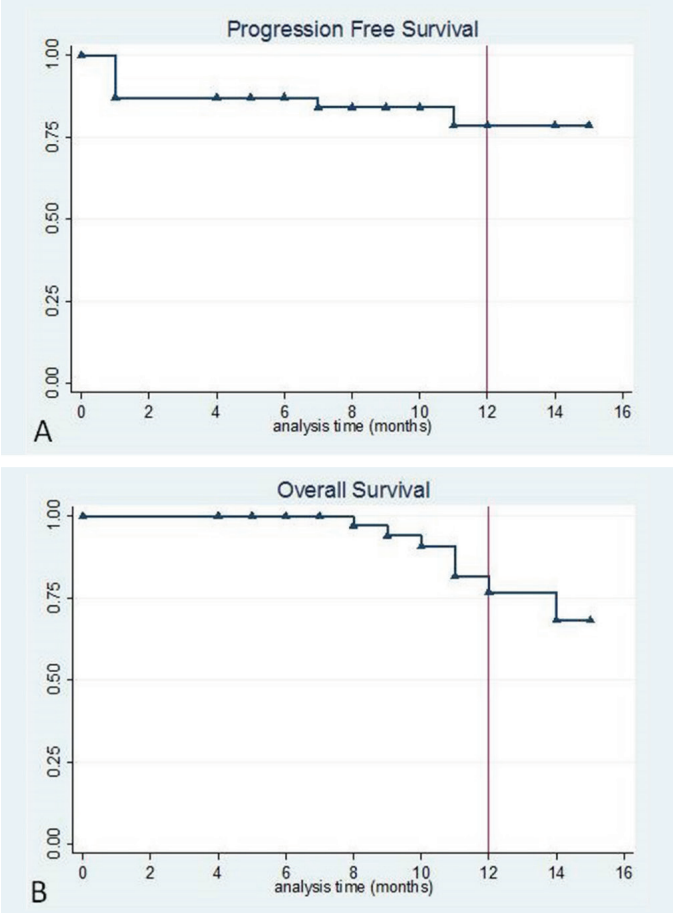

Figure 1. Kaplan-Meier survival curves: Progression free survival and overall survival of the entire cohort

The ORR was 86% in our cohort, with 37 CR and 8 PR. Two patients had SD, whereas 5 patients had PD. Regarding the patients who had stage 2 to 4 diseases, the ORR was similar (86%). The 12-month estimated OS was 76.8% and PFS was 78.5%. Compared to the historical trial [1], our CR rates in stage 2, 3, and 4 patients seem to be slightly lower (69% vs. 75%), although the overall response rates are quite similar (86% vs. 82%). Grade 3 and 4 neutropenia, which required the administration of G-CSF, was 41% in our cohort.

From the financial point of view, the rituximab biosimilar was reported to affect the outcome of DLBCL patients in the low socioeconomic group who could not afford the original molecule [16]. The main cost of the medicine was reported to be influenced by the cost of rituximab in Europe and authors concluded that cost saving could be realized with the introduction of biosimilar medications [17].

Retrospective evaluation and short follow-up period were the limitations of our study. Although biosimilar products may not always be cost-effective, its cost advantage may be an important cause of preference, apart from its safety and efficacy. The licensing of the biosimilar RED by major European and US authorities would make physicians globally

to be more comfortable with the use of drug. According to our preliminary results, RED has similar efficacy and safety with the original molecule MBT. Its noninferiority may provide commercial competition resulting in the cost advantage of original rituximab and its biosimilars. Large prospective controlled studies and more real-life data with longer follow-up are needed to document the noninferiority and safety of RED compared to MBT.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent:

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: S.K.B., M.Ö., Design: S.K.B., M.Ö., Data Collection or Processing: M.Ö., M.G.M., Ö.Ö., T.O.T., İ.Y.H., M.N.Y., M.N., S.K.B., Analysis or Interpretation: S.K.B., M.Ö., Pathological Evaluation: A.Y.A., G.Y., Writing: S.K.B., M.Ö.

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

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