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Original Research Article

Real-world use and acceptance of biosimilar rituximab in oncology practice in India

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ABSTRACT

Background: To describe the treatment patterns, patient characteristics and usage pattern of biosimilar rituximab for the treatment of Non-Hodgkin lymphomas (NHL) in India.
Methods: This real-world, retrospective, analysis included adult patients receiving biosimilar rituximab between April 2021 and March 2022.
Results: A total of 750 patients with NHL who received biosimilar rituximab were included. The most common indications reported in this analysis were diffuse large cell B-cell lymphoma [DLBCL, 64.5% (n=484)], follicular lymphoma, [FL, 23.7% (n=178)], and mantle cell lymphoma [MCL, 5.3% (n=40)]; other subtypes constituted 6.4% of the patients (n=48). The mean age of patients among DLBCL, FL and MCL was 65.5, 55.3 and 57 years, respectively. Across the lymphomas, >90% of the patients received R-chemo as first-line therapy. R-CHOP was the most common regimen across indications.
Conclusions: Biosimilar rituximab-based chemotherapy is being adopted in real-world clinical practice in India for the management of patients with B-cell NHL including DLBCL, FL, MCL and other lymphomas.

Keywords: Rituximab, Biosimilar, Lymphoma, Non-Hodgkin

INTRODUCTION

Hematologic B-cell malignancies comprise a large, heterogeneous group of lymphoproliferative disorders that range from slow-growing, indolent Non-Hodgkin's lymphomas (NHLs), such as follicular lymphoma (FL) to more aggressive forms of NHL, such as diffuse large B-cell lymphoma (DLBCL).[1,2] B-cell disorders represent >85% of all NHL cases.[3] In 2018, there were an estimated 509,590 new cases of NHL worldwide, with an estimated 248,724 patients dying from the disease, and evidence from US and UK statistics suggests that the annual incidence has been rising steadily since the 1970s.[4-6] NHL incidence rates are higher among the elderly population than in the younger population, with diagnoses of NHL being most common among patients aged 65-74 years.[7] In view of the aging population worldwide, the diagnosis and treatment of B-cell hematologic malignancies are likely to remain an important focus for the healthcare providers going forward.

NHL is a common hematological malignancy with age-adjusted incidence rates for men and women in India of 2.9/100,000 and 1.5/100,000, respectively. Within India, the incidence of NHL is several-fold higher in urban cancer registries compared to rural areas.[8] The major differences in the presentation in India versus developed countries include: median age-54 years, male gender, presence of B-symptoms in more patients, poor Eastern Cooperative Oncology Group (ECOG) performance status (≥2) at diagnosis, higher incidence of DLBCL, and a lower frequency of FL. The estimated mortality rate due to NHL is higher in India than in North America and Western Europe.[8]

Rituximab, an anti-CD20 monoclonal antibody, has shown efficacy in the treatment of various lymphoid malignancies, including B-cell NHL and CLL.[9] Rituximab

in combination with chemotherapy has shown to be more effective and generally well-tolerated as first- or second-line therapy as compared with chemotherapy alone in patients with indolent or aggressive B-cell NHL in terms of tumour remission and patient survival. Rituximab based chemotherapy regimens are included in the current treatment guidelines as first- and second-line therapy in patients with advanced-stage B-cell NHL and it is also effective as maintenance treatment in patients with indolent B-cell NHL.[10]

Biosimilar products are highly similar to biologic 'reference medicinal product' in terms of structure, functionality, immunogenicity, efficacy and safety.[11,12] The FDA grants the approval to biosimilar product with at least one indication of reference biologic product once the similarity of biosimilar product with its reference biologics is established.[13] The advent of biosimilars in oncology has led to increased access to patients with a substantially decreased cost.[14] In India, a biosimilar version of rituximab, MABTAS, was developed by Intas Pharmaceuticals Limited and was launched in 2013. The current study was conducted to present real-world evidence on the patient characteristics, and patterns of utilization associated with biosimilar rituximab in Indian clinical oncology practice.

METHODS

Study design

This retrospective analysis involved B-cell NHL patients who received rituximab biosimilar (R) based-chemotherapy at various centers across India between April 2021 and March 2022. All treatment decisions were at the investigator's discretion, including individual dose, duration of R-chemotherapy, and method and frequency of clinical assessments, in accordance with local labelling information (rituximab administered at a dose of 375 mg/m^2 body surface area, once every 3 weeks) and standard clinical practice.

The current study collected data on patient characteristics and treatment utilization patterns. The data collected included age, sex, disease stage, type of NHL, B symptoms, nodal and extranodal involvement, ECOG, medical history and details of treatment. Treatment characteristics, such as dose, dosing schedule, duration of treatment, time to rituximab biosimilar initiation, and time to therapy initiation were collected.

Sample size and statistical analysis

In this real-world study, patients' data was collected retrospectively without any predetermined sample size. The study did not test any hypothesis and only the observations from patient's records were analyzed. Demographic and baseline characteristics were summarized using descriptive statistics. Categorical variables were summarized with frequency and percentage. Continuous variables were summarized with count, mean, standard deviation, etc. Graphical presentation of data was done using bar chart as appropriate. Statistical analyses were performed using Microsoft excel (Microsoft Corp., USA).

Ethics statement

The study protocol was approved by the ACEAS independent ethics committee, Ahmedabad, India. This study was performed in accordance with good clinical practice and the ethical principles of the declaration of Helsinki. Since this study involved data retrieval from patient records only, an informed consent of patients was not obtained.

RESULTS

Overall, data of 750 patients with NHL receiving biosimilar rituximab was analyzed. The baseline characteristics of patients are summarized in Table 1. The most common diagnoses associated with use of biosimilar rituximab were diffuse large cell B-cell lymphoma [DLBCL, 64.5% (n=484)], follicular lymphoma, [FL, 23.7% (n=178)], and mantle cell lymphoma [MCL, 5.3% (n=40)]; other subtypes constituted 6.4% of the patients (n=48). The mean age of patients among DLBCL, FL and MCL was 65.5, 55.3 and 57 years, respectively. Majority of the patients across DLBCL (70.2%), FL (62.3%) and MCL (50%) were ≤60 years of age. A male preponderance was observed across the lymphoma subtypes. The mean body surface area (BSA) of the patients ranged from 1.6-1.7. B-symptoms were observed in 68%, 42% and 50% of patients among DLBCL, FL and MCL, >80% of the patients had a nodal involvement and most of the patients across the lymphoma subtypes had stage II-IV disease. The most common non-nodal sites involved were liver, spleen, bone, and central nervous system (CNS) respectively. Diabetes and hypertension were the most common comorbid conditions observed across the lymphomas.

Biosimilar rituximab treatment utilization patterns

The mean dose of biosimilar rituximab administered across DLBCL, FL and MCL was 617, 583 and 631 mg, respectively, and the median dose varied from 600-650 mg (Table 2). The median number of cycles of R-chemotherapy was 6. Among patients with DLBCL, R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride [hydroxydaunorubicin]) was administered in majority (89.9%) of the patients, followed by R-bendamustine (BR; 4.1%), dose adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; 2.5%), R-CVP (rituximab, cyclophosphamide, vincristine sulfate; 1.9%) and R-lenalidomide (0.4%). In patients with FL, R-CHOP (61.2%) and BR (35.4%) were the most commonly administered regimens, whereas in patients with MCL, R-CHOP and BR were administered in 60% and 25% patients, respectively.

Table 1: Demographic characteristics.

Parameters	All patients (n=750, 100%)	DLBCL (n=484, 64.5%)	FL (n=178, 23.7%)	MCL (n=40, 5.3%)	All others (n=48, 6.4%)
Age (Years)					
Mean ± SD	53.7±13.15	65.5±13.26	55.3±12.43	57.0±57.00	55.3±14.5
Range	17.0-86.0	17.0-85.0	22.0-86.0	28.0-78.0	21.0-80.0
>60	248 (33.1)	144 (29.7)	67 (37.6)	20 (50)	17 (35.4)
≤60	502 (66.9)	340 (70.2)	111 (62.3)	20 (50)	31 (64.6)
Gender, n (%)					
Men	527 (70.3)	355 (73.3)	112 (62.9)	32 (80)	28 (58.3)
Women	223 (29.7)	129 (26.7)	66 (37.1)	8 (20)	20 (41.7)
Height (cm)					
Mean ± SD	162.2±8.81	162.1±9.29	161.5±7.44	163.8±7.43	164.3±9.39
Range	125.0-189.0	125.0-189.0	140-179	148-183	145-186
Weight (kg)					
Mean ± SD	65.5±1.82	66.4±11.20	63.3±9.92	67.7±7.46	63.4±11.26
Range	35.0-102.0	35.0-102.0	38.0-92.0	50.0-86.0	42.0-95.0
BSA, mean ± SD	1.7±0.17	1.7±0.16	1.6±0.18	1.7±0.18	1.7±0.18
B symptoms present, n (%)					
Present	459 (61.2)	327 (67.6)	75 (42.1)	29 (72.5)	28 (58.3)
Nodal involvement, n (%)					
Nodal	618 (82.4)	407 (84.1)	147 (82.6)	33 (82)	31 (64.6)
Non-nodal	132 (17.6)	77 (15.9)	31 (17.4)	7 (17.5)	17 (35.4)
Stage at time of diagnosis, n (%)					
1	317 (42.3)	204 (42.1)	76 (42.7)	20 (50)	17 (35.4)
2	103 (13.7)	65 (13.4)	24 (13.5)	5 (12.5)	9 (18.8)
3	24 (3.2)	16 (3.3)	4 (2.2)	3 (7.5)	1 (2.1)
4	7 (0.9)	6 (1.2)	0	0	1 (2.1)
Not evaluable	299 (39.9)	193 (39.9)	74 (41.6)	12 (30)	20 (41.7)
Non-nodal site, n (%)					
Bone	108 (14.4)	72 (14.9)	28 (15.7)	5 (12.5)	3 (6.3)
CNS	19(2.5)	12 (2.5)	2 (1.1)	2 (5)	3 (6.3)
Liver	239 (31.9)	151 (31.2)	70 (39.3)	13 (32.5)	5 (10.4)
Spleen	181 (24.1)	113 (23.3)	39 (21.9)	13 (32.5)	16 (33.3)
Stage at diagnosis, n (%)					
I	128 (17.1)	88 (18.2)	32 (18)	4 (10)	4 (8.3)
II	188 (25.1)	133 (27.5)	37 (20.8)	13 (32.5)	5 (10.4)
III	196 (26.1)	123 (25.4)	57 (32)	7 (17.5)	9 (18.8)
IV	216 (28.8)	126 (26)	47 (26.4)	16 (40)	27 (56.3)
Comorbid conditions, n (%)					
Diabetes	284 (37.9)	187 (38.6)	66 (37.1)	16 (40)	15 (31.3)
Hepatic dysfunction	31 (4.1)	22 (4.5)	5 (2.8)	3 (7.5)	1 (2.1)
Hypertension	317 (42.3)	179 (37)	93 (52.2)	24 (60)	21 (43.8)
Osteoporosis	33 (4.4)	15 (3.1)	12 (6.7)	2 (5)	4 (8.3)
Renal dysfunction	27 (3.6)	18 (3.7)	8 (4.5)	0	1 (2.1)
Family history of malignancy, n (%)	23 (3.1)	15 (3.1)	7 (3.9)	0	1 (2.1)

BSA-body surface area, CNS-central nervous system, DLBCL-diffuse large B cell lymphoma; FL-follicular lymphoma; MCL-mantle cell lymphoma, SD-standard deviation.

Table 2: Treatment utilization characteristics.

Parameters	All patients (n=750, 100%)	DLBCL (n=484, 64.5%)	FL (n=178, 23.7%)	MCL (n=40, 5.3%)	All others (n=48, 6.4%)
Rituximab dose					
Mean (SD), mg	609 (91.0)	617 (78.1)	583 (91.3)	631 (133.7)	588 (155.2)
Median, mg	600	600	600	650	600
Mean (SD), mg/m^2	379 (29.4)	379 (33.4)	378 (21.9)	375 (22.4)	384 (33.4)
Median, mg/m^2	375	375	375	375	375

Continued.

Parameters	All patients (n=750, 100%)	DLBCL (n=484, 64.5%)	FL (n=178, 23.7%)	MCL (n=40, 5.3%)	All others (n=48, 6.4%)
Line of therapy (n, %)					
First-line	710 (94.7)	465 (96.1)	165 (92.7)	38 (95)	42 (87.5)
Second-line	30 (4.0)	15 (3.1)	10 (5.6)	1 (2.5)	4 (8.3)
Third-line	9 (1.2)	3 (0.6)	3 (1.7)	1 (2.5)	2 (4.2)
Other	1 (0.1)	1 (0.2)	0	0	0
Treatment regimen, n (%)					
R-Bendamustine	119 (15.9)	20 (4.1)	63 (35.4)	10 (25)	26 (54.2)
R-CHOP	573 (76.4)	435 (89.9)	109 (61.2)	24 (60)	5 (10.4)
R-CVP	21 (2.8)	9 (1.9)	8 (4.5)	2 (5)	2 (4.2)
Dose-adjusted R-EPOCH	19 (2.5)	12 (2.5)	1 (0.6)	0	6 (12.5)
R-Lenalidomide	3 (0.4)	2 (0.4)	0	1 (2.5)	0
No of cycles given					
Median (range)	6 (1-8)	6 (2-8)	6 (1-8)	6 (2-8)	6 (1-8)

DLBCL-diffuse large B cell lymphoma; FL-follicular lymphoma; MCL-Mantle cell lymphoma; R-CHOP-rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; R-CVP- rituximab, cyclophosphamide, vincristine sulfate, and prednisone; R-EPOCH-rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; SD-standard deviation.

DISCUSSION

This retrospective study reports a preliminary assessment of the real-world adoption of the biosimilar rituximab, in the Indian oncology setting. Rituximab was primarily used for treating patients with NHL which is suggestive of acceptance of biosimilar in these indications.

DLBCL and FL are the most common types among the NHLs, which is similar to that reported in our study.[15] Gogia et al evaluated the clinical characteristics, response to therapy, and the outcome of patients with DLBCL in India in a retrospective study of 267 patients.[16] The authors reported a median age of 49 years with male to female ratio of 2:1. In the current analysis, the mean age of the DLBCL patients was 65 years with male to female ratio of 2.7:1. The mean dose of rituximab was 617 mg in the current study. B-symptoms were reported in 67.6% of the DLBCL patients, which is variedly reported variably reported from other reports from India. In DLBCL patients, R-CHOP as first-line therapy is the standard of care.[17,18] In our study, most (96.1%) patients with DLBCL received treatment with R-CHOP regimen. A real-world retrospective analysis of a registry study in India by Nimmagadda et al reported that R-chemo was administered to 42.7% of DLBCL patients.[15]

In our analysis, FL was the second most common NHL after DLBCL. In an institutional analysis of FL patients, Gogia et al reported a male:female ratio of 2:1, whereas in our study, it was 2.7:1.[19] The median age reported by Gogia et al was 51 years, while it was 55.3 years in our study. Of 181 patients, R-CHOP in was given in 14 and R-bendamustine in 12 patients. In our study, R-CHOP and R-bendamustine were common regimens used in FL patients. The use of rituximab has substantially improved the outcome of patients with FL in recent years.[20]

MCL is an aggressive NHL and accounts for ~5% of the NHL patients.[21] The clinicopathological characterization of MCL is not optimal in India with only few reports available. In our analysis, the mean age of MCL patients was 57 years, which is similar to that reported by Das et al in a retrospective analysis of 51 patients with MCL. The male to female ratio was 2.4:1 whereas in our study it was 4:1, which could be attributed to the low sample size of MCL patients. Das et al reported nodal involvement in 88% patients, consistent with 82% in our study. In the study by Das et al R-chemo was given to 48% patients (R-CHOP: 30%; R-bendamustine: 14%).[21]

The treatment of cancer is a key driver for high healthcare costs.[22] In India, the cost of cancer is expected to increase as new expensive treatment modalities are being utilized widely to raise the standard of care.[23] The availability of biosimilar agents is expected to substantially improve the cost-effectiveness of cancer therapy.[24] Further, encouragement of biosimilar use through government policies and their implementation is required to realise the potential economic advantages.[25] Also, it is essential that the oncologists and patients are made aware and educated on the efficacy and safety of biosimilars.[26]

The current study findings interpretation require consideration in view of certain limitations which include missing data and potential inconsistency in data entry as multiple study centers were involved. The overall objective of our study was to determine the real-world patterns of utilization for biosimilar rituximab in India. The clinical efficacy and safety of biosimilar rituximab was not a focus of this analysis, and future research is warranted to focus on these parameters.

CONCLUSIONS

This retrospective, observational study reports the real-world usage of biosimilar rituximab, MABTAS, in Indian patients with NHL. This analysis provides a valuable

contribution to the utilization of biosimilar rituximab in various lymphomas from India. There is a need for additional data with longer follow-up periods to explore clinical outcomes and cost–effectiveness in various patient populations who may be prescribed rituximab biosimilars.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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