Efficacy and safety of biosimilar rituximab (Zytux™) in newly diagnosed patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia

Alaa Fadhil Alwan,[1] Manal Ali Abdulsahib,[2] Duaa Dhahir Abbas,[3] Saraa Ali Abdulsattar,[3] Reem Talib Ensaif[3]

[1]Department of Clinical Hematology; [2]Laboratory Department, Cytogenetic Unit; [3]Clinical Pharmacist, Department of Clinical Hematology, Pharmacy Unit, National Center of Hematology, Mustansiriya University, Baghdad, Iraq

Abstract

Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin Lymphoma (NHL) are considered parts of mature B cell neoplasms in WHO classification. They are both characterized by accumulation of B cells in blood, lymphoid tissues and bone marrow. Most of treatment protocols of NHL and CLL contain rituximab in addition to chemotherapy, which has been associated with improved survival. The aim of this study was to assess the efficacy and safety of Zytux™ (AryoGen Pharmed) in newly diagnosed patients with NHL and CLL. A prospective single center study conducted at the National Center of Hematology, Mustansiriyah University, from January 2018 till October 2018. Twenty patients were included in this study, ten of them were NHL and ten patients were CLL. All patients were treated with Zytux™ in addition to designated protocol. All patient were followed up for 6 months and evaluated at the end of each protocol. There were 20 patients in this study; the overall median age for all patients in this study was 66 years. The median age was 57.5 years for NHL and 68.5 years for CLL. There were 13 males and 7 females in total, with male predominance in both groups. Regarding safety profile, Zytux™ demonstrated similar adverse reactions in comparison to MabThera® (Roche Spa). Moreover, the overall response rate in both groups was 85% with complete response achieved in 35% and partial response in remaining 50%.This study concluded that the early results of use of Zytux™ in NHL and CLL were not inferior to reference drug MabThera® in contrast it was comparable and even better in term of safety and efficacy.

Introduction

Hematologic B-cell malignancies comprise a large, heterogeneous group of B-cell lymphoproliferative disorders in which clonal expansion of the various stages of B lymphocytes occur in bone marrow, blood or other tissues. These disorders classified according to their nature of proliferation, which range from very aggressive lymphoma to aggressive like Diffuse Large B-Cell Lymphoma (DLBCL) and slowly-growing, indolent Non-Hodgkin Lymphomas (NHL), such as Follicular Lymphoma (FL) and chronic lymphocytic leukemia. B-cell disorders represent more than 90% of all NHL and CLL cases.[1,2,3]

NHL incidence rates are higher among the elderly population than in the younger population, diagnoses of NHL is most commonly found among patients aged 65–74 years which is the same for CLL which runs slowly progressive course in which patients generally had multiple remission and relapses.[4]

As number of NHL and CLL cases are increasing because of advances in treatment and increase of aging population, therefore the treatment of these disorders will remain an important issue for health system strategy because of financial burden on the designated budget for providing chemotherapy. The management plan of NHL and CLL is depend on anti-CD20, which considered the characteristic marker for all hematological B cell neoplasms, and nowadays most international guidelines put anti-CD20 therapy like Rituximab in first line in the management of NHL and CLL. Usually the management of B-cell malignancies is determined by many factors like histologic features, staging of disease, age of patient, and the presence of comorbid disease, which can be used in international prognostic index. Staging is established using validated systems, which include Rai classification or Ann Arbor for NHL and Binet for CLL.[5,6]

Rituximab is a human/murine chimeric, glycosylated immunoglobulin (Ig) containing murine light- and heavy-chain variable region sequences, and human kappa and human IgG1 constant region sequences. Rituximab has specific affinity for the B-lymphocyte transmembrane protein, CD20, which is expressed on normal B cells (excluding stem cells, pro-B cells, and plasma B cells) and on most malignant B cells.[7] Monoclonal antibodies development requires multiple complex manufacturing processes, and therefore these high-technology products are generally expensive.[8]

The requirements of health care are growing and the increases of new and expensive health care technologies are a challenge for the sustainability of health systems worldwide. Biosimilars can be one of the solutions to reduce costs of cancer treatment, retaining the same efficacy and safety of originator drugs. In order to make these expensive targets therapy more feasible for healthcare authority and to expand its outcomes and reduce costs, biosimilar agents (molecules similar in structure, function, and safety to the original biological drugs) are introduced to the market.[9]

Zytux™ (Rituximab, AryoGen Pharmed) is biosimilar product of MabThera® (Rituximab, Roche) which has demonstrated satisfactory compatibility profile during non-clinical phase. In order to prove biosimilarity of Zytux™ to MabThera®, we have conducted this pilot study on NHL and CLL patients to compare its efficacy and safety on this subset of patients.

Materials and Methods

This is a prospective, pilot study conducted at the National Center of Hematology, Mustansiriyah University from January 2018 till October 2018. It was

Correspondence: Alaa Fadhil Alwan, Departments of clinical hematology, National Center of Hematology, Mustansiriya University, Baghdad, Iraq.
Tel.: +9647901860817
E-mail: ala_sh73@yahoo.com

Key words: Efficacy; safety; NHL; CLL.

Contributions: The authors contributed equally.

Funding: This study was funded by AryoGen Pharmed (Zytux).

Conflict of interest: There are no conflicts of interest.

Ethics approval and consent to participate: It was approved by review ethical committee of center and all patients agree and gave their written consent prior to enrollment.

Received for publication: 30 August 2019.
Accepted for publication: 30 March 2020.

Hematology Reports 2020; 12:8296
doi:10.4081/hr.2020.8296

approved by review ethical committee of center and all patients agree and gave their written consent prior to enrollment. There were 20 patients agreed to participate in this pilot study, ten of them NHL and other ten CLL.

Inclusion criteria

The inclusion criteria were age of 18 years or more, patients with CLL or NHL who are candidates to be treated with Rituximab for total therapy duration of 6 months.

Exclusion criteria

Patients were excluded from study if they had one or more of following conditions: Patients who have received MabThera® or Rituxan® out of the the study, pregnancy or lactation, severe autoimmune hemolytic anemia, current active infections or underlying diseases such as Hepatitis B or C, HIV, severe cardiac or pulmonary disorders, recent myocardial infarction, uncontrolled hypertension and epilepsy, diabetes mellitus, elevated hepatic enzyme levels (more than 2 fold ULN), serum creatinine more than 2 mg/dL, known hypersensitivity with anaphylactic reaction to chimeric monoclonal antibodies or any of study drugs.

Demographic information, medical history, physical examination, required lab tests (including CBC with differential, liver function tests, renal function tests, whole body CT, flow cytometric evaluation of CD counts and hemoglobin), especially disease staging were assessed in first visit; all efficacy and safety measures were then reassessed at each visit prior administration of chemotherapy regimen.

All patients received combination therapy with Zytux™ and chemotherapy according to designated protocols for CLL and NHL. After 3 courses reassessment was done for all patients according to disease requirements of response. Final assessments were done after 6 courses of chemotherapy protocol.

Outcomes

The primary outcome was Overall Response Rate (ORR), which is defined by the sum of Complete Response rate (CR) and Partial Response rate (PR). These were assessed following completion of scheduled chemo-immunotherapy cycles based on IWCLL (International Workshop on CLL) response criteria[10] and for NHL according to CT scan criteria for lymphoma reported by Cheson *et al*.[11]

Adverse reaction

For patient's adverse reactions evaluation was done according to NCI reference[12] using the chart below (Table 1).

Statistical analysis

Data were entered into Excel sheet and then transferred to SPSS-21 (IBM company-USA). Descriptive analysis (numbers, percentages, median, means, and standard deviation [SD]) was performed for all variables.

Results

There were 20 patients in this study; the overall median age for all patients in this study was 66 years. The median age was 57.5 years for NHL and 68.5 years for CLL. There were 13 males and 7 females in total with male predominance in both group. The other demographic and laboratory parameters for all patients are shown in Table 2.

Regarding overall response rate for all patients was 85%, for NHL group was 80% while for CLL group was 90%. In regard to complete remission, it was achieved in 50% of CLL patients with 2 patients who got negative minimal residual disease as confirmed by flowcytometry. In NHL group just 20% of patients achieved complete remission as shown in Table 3.

There were just 4 patients who experience infusion related reactions during first cycle Table 4.

Table 5 shows hematological adverse effects. Most of them were trivial and easy manageable, Table 6 shows that there was no registration of non-hematological adverse reaction during the study.

Discussion

Clinical experience with intravenously administered rituximab in B-cell hematologic malignancies is extensive, which extending to more than 20 years and to about four million patients exposed to this treatment worldwide. The requirements of health care are growing and the increases of new and expensive health care technologies are a challenge for the sustainability of health systems. Biosimilars can be one of the solutions to reduce costs of cancer treatment, keeping the same efficacy and safety of reference drugs. In order to make these expensive targets therapy more feasible for healthcare authority and to expand its outcomes and reduce costs, biosimilar agents are developed and marketed to be successful substitute. Several biosimilar rituximab has been introduced into the market, one of these is Zytux™.

The main objective of this study was to assess the safety represented by infusion related adverse events and efficacy represented by Overall Response Rate (ORR). The response to Zytux™ was compared to historical studies in which rituximab was used. As the results of this study, the efficacy of Zytux™ was comparable to rituximab in terms of ORR, therefore it is considered to be non-inferior to MabThera®. It is worth mentioning that the obtained results for ORR in our study were in agreement with various studies in the literature in which the efficacy of rituximab was assessed along with different regimens and the response rate was cited 90-95%.[13-16]

In regards to NHL group this study showed that the ORR 80% (CR 20% + PR 60%) despite short follow-up period and small sample size, this result is within the

Table 1. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0.

Grade	Definition
Grade 1	MILD, minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance
Grade 2	MODERATE, minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation
Grade 3	SEVERE and undesirable adverse events, significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation
Grade 4	Life Threatening or Disabling adverse events, complicated by acute, life threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation

NCI: National Cancer Institute Guidelines for the cancer therapy evaluation.

reported previous studies.[17-19]

In regards to CLL group this study showed that the ORR was 90% (CR 50%+ PR 40%): 2 patients got negative minimal residual disease and one patient got complete remission within 3 month and stop treatment by himself. All 3 patients above were using Benadmustine Rituximab protocol. Despite that, ORR of this study was comparable to that reported by Fischer *et al.*, but result of CR was much better than reported in Fischer study who stated that 88% had ORR and 23% had CR.[20] For those patient who were using Rituximab, Fludarabine, Cyclophosphamide protocol, the result was comparable to that reported by other studies.[21,22] The result of Zytux efficacy in CLL patients was also comparable to that reported by Iranian study in which they use Zytux™ for patient with newly diagnosed CLL with ORR 88% this is may be due to small sample size.

The other objective was to assess the safety Zytux™ in CLL and NHL, following administration of designated protocol. Infusion reactions are the most anticipated adverse reactions associated with rituximab

Table 2. Baseline demographic characteristics of all patients.

Parameter	NHL no.10	CLL no. 10	Total no. 20
Age year			
Range	17-81	46-76	17-81
Mean±SD	56.5±19.42	65.7±10.35	61.1±16.22
Median	57.5	68.5	66
Gender			
Male	6	7	13
Female	4	3	7
Staging system	Rai Stage 1= 0 Stage 2=2 Stage 3= 1 Stage 4= 7	Binet Stage A=0 Stage B= 6 Stage C= 4	
Performance status			
ECOG 0	4	1	
ECOG1	3	2	
ECOG2	3	7	
Type of NHL			
DLBCL	7		
FL	2		
Type of treatment protocol	R-CHOP=9 R-COP =1	RFC=3 RB= 4 REP= 3	
Splenomegaly	6	6	12
Hepatomegaly	3	5	8
Lymphadenopathy	9	8	17
Hematological profile			
Mean Hemoglobin (range)gm/dL	11.89 (8.8-18)	12.7 (10-14)	12.34 (8.8-18)
Mean Leucocytes (range) $x10^9/L$	8.69 (2.2-24)	69 (19-180)	38.845 (2.2-180)
Mean Platelets (range) $/mm^3$	208000 (81000-461000)	192400 (86000-414000)	200150 (81000-461000)
Liver disease	0	0	
Cardiac disease	Heart failure=1	IHD =3 CMP=1 HT=1Stroke =1	7
Renal disease	0	0	0
Others	Hepatitis B+ve	DM=1	2

Table 3. Clinical response rates.

Response	NHL (10 patients) (%)	CLL (10 patients) (%)	NHL+CLL (20 patients) (%)
Overall response rate	8 (80)	9 (90)	17 (85)
Complete response	2 (20)	5 (50)	7 (35)
Partial response	6 (60)	4 (40)	10 (50)
No response	2 (20)	1 (10)	3(15)

Table 4. Incidence of infusion-related reactions for Zytux™.

Infusion Cycle	NHL group	CLL group	Overall
First cycle	2	2	4
Subsequent cycles	1	0	1

administration, especially during the first cycle of treatment, this study showed that just 4 patient (20%) experienced mild infusion reaction grade 1 and 2 in which all of them completed the dose of Zytux™ after giving steroid and paracetamol. It has been reported that MabThera®infusion reactions may reach up to 77% of patients at early stages of the first cycle of infusion,[23] but in other study it reach up to 35% and because less in subsequent cycles.[24] The difference in reported infusion relate reaction between this study and that in the literature could be due to exact implementation of infusion protocol and close monitoring applied for patient setting. The most occurred reactions in the current study were chills, nausea and hot flashes.

Hematologic adverse reactions induced by chemotherapy regimens are of particular importance as they are directly associated with patient's quality of life and treatment outcomes. Regarding these facts, the safety profile of biosimilar products concerning hematologic toxicities needs to be closely considered. The results of the current study demonstrated that there were no statistically

Table 5. Hematologic adverse reactions of Zytux™.

Hematologic adverse reactions	NHL, 10 patients	CLL, 10 patients	Overall, 20 patients (%)
Thrombocytopenia			
Grade I (<150000 to 75,000/mm^3)	3	5	8
Grade II (50,000 to 75,000/mm^3)	0	1	1
Grade III (25,000 to 50,000/mm^3)	0	0	0
Grade IV (<25,000/mm^3)	0	0	0
Total	3	6	9 (45)
Anemia (hemoglobin level)			
Grade I (<12 to 10 g/dL)	3	2	5
Grade II (8.0 to 10.0 g/dL)	2	1	3
Grade III (<8.0 g/dL)	0	0	0
Total	5	3	8(40)
Neutropenia			
Grade I (<4000 to 1500/mm^3)	7	10	17(85)
Grade II (1000 to 1500/mm^3)	1	1	2
Grade III (500 to 1000/mm^3)	1	0	1
Grade IV (<500/mm^3)	0	0	0
Total	9	11	20(100)

Table 6. Type of non-hematologic adverse reactions for Zytux™.

Adverse reaction	NHL Grade		CLL grade		Both, any grade
	1+2	3=4	1+2	3+4	
Cardiovascular					0
Peripheral edema					
Hypertension					
Hypotension					
Gastrointestinal					0
Nausea					
Diarrhea					
Abdominal pain					
Dermatologic					0
Skin Rash					
Pruritus					
Night sweats					
Neuromuscular and skeletal					0
Weakness					
Muscle spasm					
Arthralgia					
Central nervous system					0
Fatigue					
Chills					
Headache					
Neuropathy					
Insomnia					
Pain					
Respiratory					0
Cough					
Shortness of breath					
Pharyngitis					
Infection					0
Hepatic					0
Increased ALT/SGPT					
Endocrine and metabolic					0
Weight gain					
Others					

or clinically meaningful diversity between Zytux™ and MabThera® according to the hematologic toxicities. The hematologic events were in line with literature in terms of frequency and intensity, and none of the events led to therapy discontinuation.

For non-hematologic adverse reactions, this study did not recorded any of these as shown in Table 5 in contrast to many other studies which showed that some patients may got renal or cardiac adverse event.[23] We think that the short follow-up and design of study lead to this result.

The limitations of this study included small sample size and lack of survival information of patients because the complete follow-up still going on.

Conclusions

This study concluded that the early results of use of Zytux™ in NHL and CLL was not inferior to reference drug MabThera® in contrast it was comparable and even better in term of safety and efficacy, and our recommendation is to conduct head to head, multicenter study with larger sample size to confirm these results.

References

1. Boffetta P. Epidemiology of adult non-Hodgkin lymphoma. Ann Oncol 2011;22:iv27–iv31. doi: 10.1093/annonc/mdr167.
2. Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. Am J Hematol 2015;90:446-60. doi: 10.1002/ajh.23979.
3. Rashid NG, Abdallah BK, Al Ani MH, Yassin AK. Demographics and outcome of diffuse large B-cell lymphoma patients in Hiwa Hospital - Iraq-Kurdistan-Sulaimani. Iraqi J Hematol 2018;7:55-61
4. Gribben JG. How I treat CLL up front. Blood 2010;115:187-97. doi: 10.1182/blood-2009-08-207126.
5. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v83–90.
6. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v78–84.
7. Candelaria M, Gonzalez D, Fernández Gómez FJ, et al. Comparative assessment of pharmacokinetics, and pharmacodynamics between RTXM83™, a rituximab biosimilar, and rituximab in diffuse large B-cell lymphoma patients: a population PK model approach. Cancer Chemother Pharmacol 2018;81:515-27
8. Shaughnessy AF. Monoclonal antibodies: magic bullets with a hefty price tag. BMJ 2012; 345:e8346.
9. Bennett CL, Chen B, Hermanson T, et al. Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncol 2014;15:e594-e605
10. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-60.
11. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25: 579-86.
12. Colevas AD, Setser A. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 is the new standard for oncology clinical trials. J Clin Oncol 2004;22: 6098.
13. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced- stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106: 3725–32.
14. Vose JM, Link BK, Grossbard ML, et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol 2001;19:389–97.
15. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–42.
16. Robak T, Dmoszynska A, Solal-Céligny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28: 1756–65.
17. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomized study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013–22.
18. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23: 4117–26.
19. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab- CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040–5.
20. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209–16.
21. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112: 975–80.
22. Foon KA, Boyiadzis M, Land SR, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high-dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27: 498–503.
23. Rituxan (rituximab) injection, for intravenous use. Genentech, South San Francisco. 2016. Available from: https://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed 21 August 2018.
24. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070-8.