International Journal of Community Medicine and Public Health
Bin Sabbar NS et al. Int J Community Med Public Health. 2019 Oct;6(10):4199-4203
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: http://dx.doi.org/10.18203/2394-6040.ijcmph20194475

Original Research Article

Addition of rituximab to hyper-CVAD improves overall survival in newly diagnosed Burkitt leukemia/lymphoma from the Middle East and North Africa region

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Received: 31 July 2019
Accepted: 07 September 2019

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ABSTRACT

Background: Burkitt leukemia/lymphoma (BL) is a highly aggressive malignancy treated with intensive combinational chemotherapy. However, there is paucity in the literature with regards to outcome in patients with BL from the Middle East and North Africa Region (MENA).
Methods: We examined the impact of incorporation of the monoclonal antibody rituximab within a chemotherapy backbone of hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine and methotrexate (hyper-CVAD). Between 2007 to 2016, a total of 21 patients were identified and data retrospectively collected with median follow up was 32 months (1.1-120). The cohort was stratified based on exposure to rituximab and there was no significant difference regarding gender, age, stage, presence of constitutional symptoms, baseline presenting blood counts and proportion of patients completing prescribed therapy regimen between the strata.
Results: Estimated overall survival (OS) of the entire cohort at 2 years was 71.1%; however, patients who received rituximab in conjunction with hyper-CVAD had a statistically significant improvement in 2-year OS at 81.2% vs 40% (p=0.048).
Conclusions: In conclusion, we observed that incorporation of rituximab within a hyper-CVAD backbone improved OS in BL patients from the MENA region. These results warrant further evaluation.

Keywords: Burkitt lymphoma, Hyper-CVAD, Rituximab

INTRODUCTION

Burkitt leukemia/lymphoma (BL) is a highly aggressive mature B-cell non-Hodgkin lymphoma (NHL) arising from the germinal center. It often presents as one of three distinct clinical entities; endemic (African), sporadic and immunodeficiency associated with variable epidemiologic, clinical presentations and genetic features.[1] The disease can manifest in a leukemic or lymphomatous state but both are considered different manifestations of the same disease as per the World Health Organization (WHO) update.[2] The histological presentation reveals sheets of monomorphic medium sized cells with intensely basophilic cytoplasm and high proliferative index Ki67 approaching 100%. At the genetic level, the cells exhibit rearrangements involving the MYC gene on chromosome 8 detected by conventional cytogenetics or fluorescence in situ hybridization (FISH). The neoplastic cells express IgM and immunoglobulin light chain restriction, B-cell markers (CD19, CD20, CD22, and CD79a), germinal center antigens (CD10 and BCL6) and lack expression of TdT, BCL2 and CD5. Given the rarity of this disease and

high curative potential of available therapies, advances in therapy over the years have been limited.

The highly proliferative nature of BL renders it susceptible to high intensity combinational chemotherapy. The backbone of therapy is comprised of multi-agent chemotherapy with adequate central nervous system (CNS) prophylaxis. Three main approaches to therapy are used in adult patients; short duration of intensive combinational chemotherapy, stepwise induction followed by consolidation and maintenance in an acute lymphoblastic leukemia (ALL) like therapy and infusional chemotherapy such as dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH). For adult patients, the bulk of evidence and clinical experience is with short and intensive treatment e.g., cyclosphosphamide, doxorubicin, vincristine and high dose methotrexate (CODOX-M) alternating with ifosfamide, cytarabine, etoposide, and intrathecal methotrexate (IVAC) with over two thirds of patients achieving long term remission.[3-5] Another regimen consisting of cyclophsophamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine (hyper-CVAD) with CNS prophylaxis as reported by the MD Anderson cancer center with 49% of patients being alive at 3 years.[6] Hematologic toxicity with Hyper-CVAD was high despite the use of growth factor support and febrile neutropenia occurring in 86% of patients. Older patients whom are less fit for such intensive therapies may benefit from dose adjusted EPOCH with very promising results in small case series.[7]

Rituximab incorporation within the chemotherapy backbone has proven to be a highly successful strategy in the treatment of diffuse large B-cell lymphoma resulting in improvement in event free and overall survival.[8] Given such experience and a similar expression of CD20, there has been a long standing interest in attempting to replicate such results in patients with BL. Furthermore, literature regarding lymphoma in general and BL in particular from the Middle East and North Africa Region is limited. Our aim from this analysis is to determine whether the incorporation of rituximab in a hyper-CVAD chemotherapy backbone improves overall survival in a homogenous patient population of BL treated at our center.

METHODS

Study design and patients

This is a single center study conducted at King Abdulaziz Medical City (KAMC), a tertiary care academic hospital with over 1500 bed capacity in Riyadh, Saudi Arabia. After institutional review board (IRB) approval, patients ≥14 years of age with a diagnosis of BL from January 2008 until December 2016 were identified through a query of the institutional Oncology database. Diagnosis of BL was per the World Health Organization 2016 Classification and based on a combination of compatible morphology, immunophenotype and genetic profile.[2] Selection criteria included newly diagnosed patients with BL whom received front line therapy with Hyper-CVAD with or without the monoclonal antibody rituximab. Patients whom received an alternative treatment plan, including palliative treatment were excluded for homogeneity of the study population. All clinical and pathological data were extracted and collated retrospectively.

Treatment protocol

All patients were treated with Hyper-CVAD given in alternating cycles (A and B) with cycle A consisting of 300 mg/m^2 of intravenous (IV) cyclophosphamide every 12 h on days 1-3 for a total of 6 doses with appropriate mesna dose for bladder protection; vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV for two days (day 1 and 11); doxorubicin 50 mg/m^2 IV on day 4 followed by dexamethasone 40 mg IV on days 1-4 then 11-14. Cycle B contained high dose methotrexate 1 g/m^2 given over 24 h on day 1 with appropriate hydration with sodium bicarbonate, leucovorin and therapeutic drug monitoring; cytarabine 3000 mg/m^2 IV over 2 h given every 12 h on days 2-3 for a total of 4 doses and methylprednisolone 50 mg IV every 12 h on days 1-3. A full course of treatment consisted of 4 cycles each of alternating therapy. Central nervous system prophylaxis consisted of intrathecal (IT) methotrexate 12 mg and hydrocortisone 50 mg given on day 2 and cytarabine 50 mg on day 8 of cycles A and B. The monoclonal antibody rituximab was given on day 1 of each cycle (A and B) with a dose of 375 mg/m^2. The decision with regards to rituximab administration was at the discretion of the treating physician.

Definitions and statistical analysis

Baseline patient, disease, and treatment-related variables were reported using descriptive statistics (frequency, median, and percentage). Categorical and continuous variables were compared using the Pearson and Wilcoxon or Kruskal-Wallis tests, respectively. Estimates of OS and PFS were computed using the Kaplan-Meier method and reported as a percentage. Group comparisons were made using the log-rank test. OS was calculated as the time from diagnosis until death from any cause or last documented follow-up. Statistical analysis was performed using JMP pro version 11 (SAS Institute, Cary, NC) software.

RESULTS

Patient characteristics

A total of 32 cases were identified through query of the oncology database at our center. Eleven patients were treated with protocols other than hyper-CVAD (including three patients receiving palliative therapy). Thus, a total of 21 patients treated with hyper-CVAD with or without rituximab were included for further analysis.

The median age at diagnosis was 40 years (14-67) with 12 (57%) being male. Lymphoma was the most common presentation in 15 (71%) patients, whereas the remaining 6 (29%) presented with leukemic phase disease. Stage at presentation was I in 4 (19%), II in 4 (19), IV in 7 (33%) and N/A (leukemic presentation) in the remaining 6 (29%) patients. Median (range) of presenting white blood count (WBC), hemoglobin (Hb) and platelet count (plt) were 8.9 (42.9-0.8) × 10^9/l, 124 (164-77) g/l and 272 (429-11) ×10^9/l, respectively. Rituximab was used in 16 (76%) of patients and 16 (76%) completed a full course of therapy consisting of 4 alternating cycles each of parts A and B of hyper-CVAD in addition to CNS prophylaxis. The median follow up was 31.9 months (1.1-120) and at last follow up a total of 6 (29%) of patients had died; 3 due to sepsis while on therapy while the remaining 3 due to progression. The median time to death due to progression was 4.3 months (3.2-7.2).

Outcome stratified by therapy

Rituximab was given to a total of 16 (76%) of patients, and baseline characteristics stratified by rituximab treatment are shown in Table 1. There was no significant difference with regards to patients' characteristics including gender, age, stage, presence of constitutional symptoms, baseline presenting blood counts and proportion of patients completing prescribed therapy regimen. There was a trend towards higher incidence of Burkitt lymphoma vs leukemia in the cohort receiving rituximab (p=0.09). Estimated OS of the entire cohort at 2 years was 71.1%. Patients receiving R-hyperCVAD had a significant improvement in 2-year OS at 81.2% compared to 40% for those who did not receive the drug (p=0.048).

Table 1: Baseline characteristics stratified by rituximab therapy.

Characteristic	Rituximab group (n=16)	No rituximab group (n=5)	P value
Male, N (%)	9 (56)	3 (60)	0.88
Age (years), median (range)	36.5 (17-67)	44 (13-48)	0.8
Subtype, N (%)			
Lymphoma	13 (81)	2 (40)	0.09
Leukemia	3 (19)	3 (60)	
Stage (lymphoma), N (%)			
I	3 (18)	1 (20)	0.13
II	3 (18)	1(20)	
IV	7 (44)	0	
N/A	3 (19)	3 (60)	
B-symptoms, N (%)			
Yes	4 (25)	2 (40)	0.53
No	12 (75)	3 (60)	
Baseline counts, median (range)			
WBC (10^9/l)	10.3 (1.7-42.9)	4.5 (0.8-18.3)	0.32
Hb (g/l)	127 (82-162)	96 (77-164)	0.74
Plt (10^9/l)	283 (11-429)	272 (24-363)	0.46
Completed therapy	13 (81)	3 (60)	0.35

N/A: not applicable; B: symptoms, constitutional symptoms; WBC: white blood count; Hb: hemoglobin; Plt: platelet.

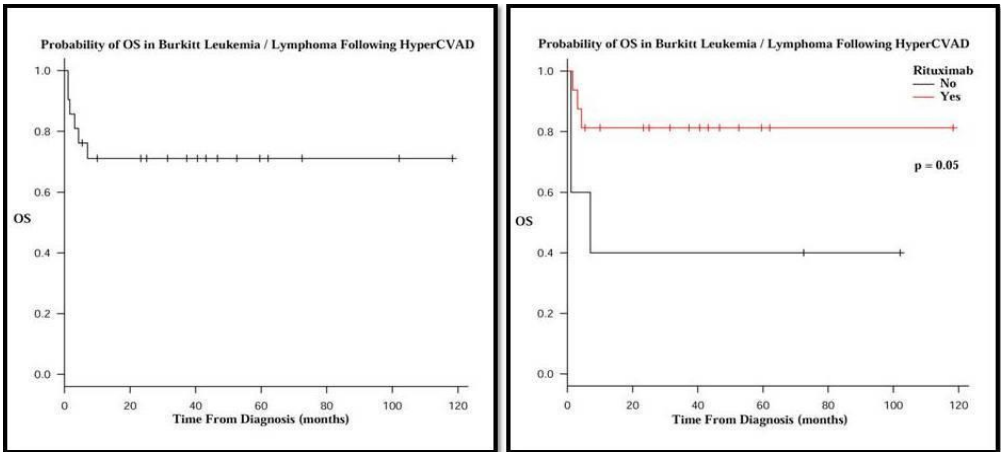

Figure 1: Overall survival following hyper-CVAD in Burkitt leukemia/lymphoma stratified by rituximab therapy.

DISCUSSION

Progress in the treatment of BL has been hampered by the relative rarity of this disease and heterogeneity of published literature with regards to baseline characteristics of study subjects and therapies utilized. Such paucity of the literature is further compounded in regions with limited outcome reports such as the MENA region. In this study we sought to determine whether the incorporation of the anti CD20 monoclonal antibody rituximab to a hyper-CVAD chemotherapy backbone would improve OS for newly diagnosed BL patients. We observed that at 2-years, the OS was significantly better for the R-hyper-CVAD arm compared to hyper-CVAD alone at 81.2% vs. 40%, respectively. Previously, Cortes et al, reported a single center experience at the MD Anderson of immunodeficiency associated BL using hyper-CVAD and observed a 2-year survival of 48%.[9] Subsequently, the same group incorporated rituximab within the same backbone treating a total of 28 patients and observed a 3-year OS of 89%.[10]

Two important prospective studies shed important light into this issue. The first was by the German multicenter study group for adult acute lymphoblastic leukemia where over 363 adult patients received a total of 8 doses of rituximab within a multiagent chemotherapy backbone of high dose methotrexate, high-dose cytosine arabinoside, cyclophosphamide, etoposide, ifosphamide, corticosteroids, and triple IT therapy.[11] An impressive 5 year OS of 80% was observed suggestive of a very high curative potential of this regimen. More recently, a phase 3 trial across 45 centers in France randomized 260 patients to rituximab vs. placebo within a chemo backbone and observed a favourable hazard ratio for the treatment arm with HR 0.59 (0.38-0.94; p=0.025). Collectively, these results support the use of rituximab to further improve the outcome of BL. However, whether these findings can be extended to patients of other ethnic backgrounds remained unknown.

Our study has some important limitations, particularly with regards to its sample size and retrospective nature. However, a number of important learning points ought to be highlighted; first, to our knowledge, this is the first study examining this matter using homogenously treated patients from the MENA region from the same ethnic background. Second, the duration of follow up was adequate to detect the majority of events that typically occur within one year in this disease. Lastly, we observed a similar outcome within this cohort to the reported literature from various centers. In conclusion, we observed that incorporation of rituximab within a hyper-CVAD backbone improved OS in BL patients from the MENA region. These results warrant further evaluation.

ACKNOWLEDGEMENTS

We would like to thank everyone who helped with this research.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional review board of the King Abdullah International Medical Research Center, National Guard Health Affairs, Riyadh, Saudi Arabia

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Cite this article as: Bin Sabbar NS, Alowirdi FS, Basakran FA, Al-Badr LA, Assiri RA, Alshahrani WA, et al. Addition of rituximab to hyper-CVAD improves overall survival in newly diagnosed Burkitt leukemia/lymphoma from the Middle East and North Africa region. Int J Community Med Public Health 2019;6:4199-203.