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blood advances

Rituximab for children with EBV-positive Burkitt lymphoma in East Africa

William Frank Mawalla,[1] Caroline Achola,[2] Hadijah Nabalende,[2] Isaac Otim,[2] Ismail D. Legason,[2] Martin D. Ogwang,[2] Pamella M. Aol,[2] Godlove Sandi,[3] Hadija Mwamtemi,[3] Salama Mahawi,[3] Elifuraha Mkwizu,[4] Philomena G. Lyamuya,[4] Jacqueline P. Kamanga,[5] Kristin Schroeder,[5] Paul Ntemi,[5] Clara Chamba,[1] Dimitris Vavoulis,[6] Liz Morrell,[7] Lulu Chirande,[1] and Anna Schuh[1,6]

[1]Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; [2]Oncology Unit, St Mary's Hospital Lacor, Gulu, Uganda; [3]Paediatric Oncology Unit, Muhimbili National Hospital, Dar es Salaam, Tanzania; [4]Cancer Care Centre, Kilimanjaro Christian Medical Centre, Moshi, Tanzania; [5]Department of Oncology, Bugando Medical Centre, Mwanza, Tanzania; [6]Department of Oncology, University of Oxford, Oxford, United Kingdom; and [7]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

Key Points

- Incorporating rituximab into the INCTR chemotherapy protocol for treating EBV-positive BL in Sub-Saharan Africa is both feasible and safe.
- The addition of rituximab to the INCTR protocol significantly improves survival in EBV-positive BL children in Sub-Saharan Africa.

The addition of rituximab to the chemotherapy backbone was shown to significantly improve outcomes of children with aggressive high-grade lymphomas in high-income countries. However, data on its safety and efficacy in children with Epstein-Barr virus (EBV)–positive Burkitt lymphoma (BL) are limited. We conducted a prospective nonrandomized observational study in East African patients aged ≤25 years with confirmed BL. Patients received either the International Network for Cancer Treatment and Research (INCTR)–based standard chemotherapy (cyclophosphamide, vincristine, and methotrexate [COM]) or rituximab plus standard chemotherapy (R-COM). The primary end point was safety. The secondary outcomes were event-free and overall survival and cost-effectiveness of incorporating rituximab. Primary analyses were conducted in the intention-to-treat population. The median follow-up was 23 months. Safety analyses included 72 patients: 32 in the COM group and 40 in the R-COM group. Grade ≥3 adverse events occurred in 18% of R-COM patients and 16% of COM patients. With respect to treatment outcomes at 12 months, 5 events were observed in the R-COM group and 14 in the COM group. The 12-month event-free survival was 67% with R-COM and 43% with COM (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.24-0.98; P = .045). There were 8 deaths in the R-COM group, whereas 16 patients died in the COM group (HR, 0.32; 95% CI, 0.14-0.75; P = .009). R-COM was particularly effective in advanced-stage disease. The addition of rituximab to the INCTR-based protocol (COM) for EBV-positive BL has been observed to be safe and feasible in experienced centers in East Africa and saves lives.

Introduction

Burkitt lymphoma (BL), a mature B-cell lymphoma, is the predominant cancer among children in Sub-Saharan Africa (SSA).[1,2] Unlike sporadic cases in resource-rich regions, BL in SSA is predominantly

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Deidentified individual participant data underlying the reported results will be made available upon publication of this study. Access will be granted to approved study proposals with a signed data access agreement. The study protocol is available in the Supplementary data. For data access requests, please contact the corresponding author, William Frank Mawalla (mawallawf@ymail.com).

The full-text version of this article contains a data supplement.

driven by the Epstein-Barr virus (EBV) and manifests aggressively, resulting in poor outcomes.[2,3] Over the past 3 decades, significant efforts have been made in treating aggressive mature B-cell lymphomas in high-income regions, leading to a remarkable 90% cure rate for BL in those areas.[4,5]

However, given the lack of supportive care and cost constraints in SSA, in 2004, the International Network for Cancer Treatment and Research (INCTR) proposed a more feasible standard treatment regimen for equatorial SSA countries.[6,7] This regimen, adopted by many equatorial SSA countries, such as Tanzania and Uganda, includes cyclophosphamide, vincristine, and methotrexate (COM), along with intrathecal methotrexate and cytarabine for Central Nervous System (CNS) prophylaxis. Limited data on toxicity and outcomes exist for the INCTR protocol, with overall survival (OS) rates reported at 67% and 62% at 1 and 2 years, respectively.[7]

Many attempts to improve outcomes of children with advanced BL in SSA through dose intensification have failed due to lack of supportive care.[8-11] Most recently, the Groupe Francophone d'Oncologie Pédiatrique - Lymphomes Malins B 2009 (GFA-LMB2009) protocol has shown that rapid induction, including the addition of high-dose methotrexate to cyclophosphamide, vincristine, and prednisolone (COP), might be beneficial, although Complete Remission (CR) rates of 49% before dose intensification were disappointing, and only 58% of children completed treatment.[8]

Although fully adopting the intensive BL protocols[12-17] used in high-income countries requires investment into supportive care, integrating rituximab, an established and highly effective agent in B-cell lymphomas that is also increasingly available in many resource-restricted health care systems, as a biosimilar into the existing INCTR protocol is anticipated to enhance its efficacy and minimize adverse effects. However, data on the safety, efficacy, and feasibility of rituximab in children with EBV-positive BL in SSA settings are currently lacking.

Given the demonstrated benefit of rituximab for children with BL in high-income settings,[18-20] we felt that a randomized controlled trial would be ethically challenging and unfeasible in our context. This decision was influenced by existing evidence supporting rituximab's efficacy, significant resource constraints in our setting, and the urgent need to improve patient outcomes. Therefore, we adopted a nonrandomized, observational design to pragmatically evaluate the safety and feasibility of adding rituximab to the existing INCTR-based protocol.[5]

Methods

Study oversight

This study was conducted as part of the Aggressive Infection–Related East African Lymphoma (AI-REAL) consortium spanning 1 recruitment site in Uganda and 3 recruitment sites in Tanzania. Prospective recruitment of children for extensive sample and clinical data collection started in 2019. After the publication of results using rituximab in high-risk, high-grade childhood lymphoma, all patients recruited into the AI-REAL study were offered rituximab in addition to chemotherapy as the new gold standard.[5] The study sponsor was the University of Oxford. Funding was provided by the UK National Institute of Health Research Global Health Programme. Roche Kenya supported commercial supplies of rituximab but had no role in the design, conduct, or preparation of the manuscript.

Parents and patients (if age appropriate) signed informed consent and assent forms before enrolment. Ethical approval was granted by the following institutions: the Oxford Tropical Research Ethics Committee (reference, 15-19), the National Institute of Medical Research (NIMR/HQ/R.8a/Vol.IX/3408) in Tanzania, the Uganda National Council of Science and Technology (HS529ES), and the Lacor Hospital Institutional Research Ethics Committee (074/05/19) in Uganda. An international, independent advisory board, which included 2 pediatric oncologists and 1 statistician, monitored progress.

Study design

This was a prospective, nonrandomized observational study involving patients who enrolled in the AI-REAL study to assess the impact of adding rituximab to the standard chemotherapy regimen in patients with BL. Although a randomized controlled trial could provide high-quality evidence, we felt it was not feasible in this context due to ethical concerns about withholding rituximab, which is supported by existing evidence of efficacy and safety in high-income settings.

R-COM group. This involved patients with BL who received rituximab in addition to the standard chemotherapy COM regimen (R-COM), along with intrathecal methotrexate and cytarabine for CNS prophylaxis.

COM group. This included patients who only received the standard COM regimen, along with intrathecal methotrexate and cytarabine for CNS prophylaxis. Recruitment of patients into COM and R-COM groups partially overlapped due to delays in the introduction of rituximab in some study sites and interruptions in the supply of rituximab during certain periods of the study (supplemental Figure 1). No obvious changes in the availability or quality of supportive care measures were observed during the recruitment period.

Patients

Eligible patients were aged 3 to 25 years with newly diagnosed histologically confirmed BL. Tissue was assessed by 3 independent study pathologists according to the modified Naresh algorithm.[21,22] Clinical staging at Muhimbili National Hospital, Kilimanjaro Christian Medical Centre, and Bugando Medical Centre in Tanzania was by neck, chest, abdominal, and pelvic computed tomography (CT) scans, bone marrow aspirate, and lumbar puncture. Clinical staging in St Mary's Hospital Lacor, in Northern Uganda, was by ultrasound scan, chest X-ray, bone marrow aspirate, and lumbar puncture.

Treatment

Patients in the COM arm received standard INCTR-based chemotherapy (cyclophosphamide, 1200 mg/m^2; vincristine, 1.4 mg/m^2; methotrexate, 75 mg/m^2). The R-COM arm received rituximab (375 mg/m^2) plus standard chemotherapy (R-COM). Both regimens were given biweekly for 6 cycles. Additionally, CNS prophylaxis with intrathecal methotrexate and cytarabine was administered based on age: methotrexate 8 mg for patients aged <2 years, 10 mg for 2 to 3 years, and 12 mg for >3 years; cytarabine 35 mg for patients aged <2 years, 40 mg for 2 to 3 years, 50 mg for >3 years.

Early response evaluation was performed by clinical examination after 2 cycles of COM or R-COM. Children with residual disease at this time point were classified as having primary refractory disease and switched to second-line treatment with ifosfamide 1500 mg/m^2, etoposide 60 mg/m^2, and cytarabine 100 mg/m^2 (IVAC) or rituximab 375 mg/m^2, ifosfamide 1500 mg/m^2, etoposide 75 mg/m^2, and cytarabine 100 mg/m^2 (R-IVAC) combinations. Children without evidence of residual disease received COM or R-COM for 4 more cycles, completing 6 cycles. No high-dose methotrexate was given.

Rituximab administration, management of infusion-related side effects, and tumor lysis prevention followed agreed local protocols. Briefly, rituximab was administered as an IV infusion (at a dose of 375 mg/m^2) on day 1 of each cycle for a total of 6 doses. Consecutive cycles were administered as soon as blood counts recovered and the patient's condition allowed.

End points

The primary end point was safety. Analysis of safety was performed on an intention-to-treat (ITT) basis, defined as any patient who was either considered for COM or R-COM treatment, irrespective of the number of cycles received. Patients who switched from COM or R-COM to dose intensification because of primary refractoriness were also included in this safety analysis. Because this was a nonrandomized study, patients were censored for the ITT analysis at the time of the decision to initiate treatment with either COM or R-COM, depending on the availability of rituximab at the time.

Safety was assessed by the number and seriousness (grade 3 and 4) of adverse events and was documented using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5. Adverse events of special interest included infusion-related reactions. Grade 3 or 4 adverse events or treatment-related deaths during and after 6 cycles of treatment were recorded. Three experienced clinicians were engaged to evaluate all data about the death of patients in the study. They were tasked to determine the cause of death, categorized as treatment related, disease related, other cause, or indeterminable.

The secondary end points were as follows: (1) event-free survival (EFS), which was defined as the minimum time between diagnosis and either the detection of residual tumor after receipt of the second cycle of therapy (ie, primary refractory disease), relapse, progressive disease, second cancer, death from any cause, or last follow-up for patients who did not have any event; (2) OS, which was defined as the time from diagnosis to either death or last follow-up for patients who did not have any event; and (3) the cost-effectiveness of incorporating rituximab into standard chemotherapy, modeled by the use of locally derived clinical study and cost information (not reported here in detail).

We also conducted a per-protocol (PP) analysis for patients who completed at least 6 cycles of COM or R-COM without switching to a more intensive second-line regimen, with or without rituximab, during their treatment course (supplemental Figures 2 and 3).

Investigators evaluated treatment response and outcomes by conducting assessments through physical examinations, chest radiography, abdominal sonography, and CT scans. Notably, Positron Emission Tomography (PET) scans were unavailable in Tanzania and Uganda throughout the study duration.

Statistics

We considered R-COM safe if <25% of patients experienced any grade ≥3 adverse side effects that can be attributed to the administered therapy. With 40 patients, at least 16 of them (40%; 95% confidence interval [CI], 24.9-56.7) would need to experience adverse effects for R-COM to be deemed unsafe. Similarly, using the same assumptions for COM, at least 13 of 32 patients (40.6%; 95% CI, 23.7-59.4) would need to experience grade ≥3 adverse side effects for it to be considered unsafe. Categorical and continuous variables were summarized with frequencies and medians (with interquartile ranges [IQRs]). Differences between the COM and R-COM groups were assessed with an exact Wilcoxon rank-sum test for continuous variables and χ^2 test (Fisher exact tests were used when cell numbers were <5) for categorical variables. EFS and OS were estimated using Kaplan-Meier curves, and the log-rank test was used to assess differences between the COM and R-COM groups in those who completed 6 cycles. All reported *P* values are 2-sided, without adjustment for multiple comparisons.

Statistical analyses were done with R statistical software (http://www.R-project.org/).

Sensitivity analysis

Two patients were lost to follow-up early in the study after receiving only 1 dose of COM or R-COM, which provided insufficient data for meaningful evaluation. To assess the potential impact of their exclusion on the study's findings, we conducted a sensitivity analysis under 2 scenarios. In the first scenario, these patients were censored at the time of their last follow-up. In the second scenario, they were included as events, assuming death at 8 months for the R-COM patient and 1 month for the COM patient, based on the median survival time of patients with events in their respective treatment groups. This analysis aimed to evaluate the robustness of the study's findings in relation to these missing data.

Results

Analysis sets

From 1 May 2019 to 25 September 2022, a total of 80 patients diagnosed with BL and treated with either standard therapy (COM) or rituximab plus standard therapy (R-COM) were enrolled. For the ITT analysis, 8 patients were excluded: 6 withdrew consent, and 2 were lost to follow-up. For the PP analysis, 6 patients from the COM group and 17 from the R-COM group were excluded due to switching after at least 2 cycles of their first-line regimen. Thus, the PP analysis included 49 patients in total, 26 in the COM arm and 23 in the R-COM arm (Figure 1).

Patients and treatment

At baseline, the patient characteristics were largely comparable between the 2 treatment groups (Table 1), although higher proportion of patients presented with advanced-stage disease in the COM group (69%) than the R-COM group (48%).

Adverse events

The median duration of first-line treatment was higher in the R-COM group (15 weeks) than the COM group (10 weeks; $P = .023$; Table 2). The median number of treatment cycles was also higher

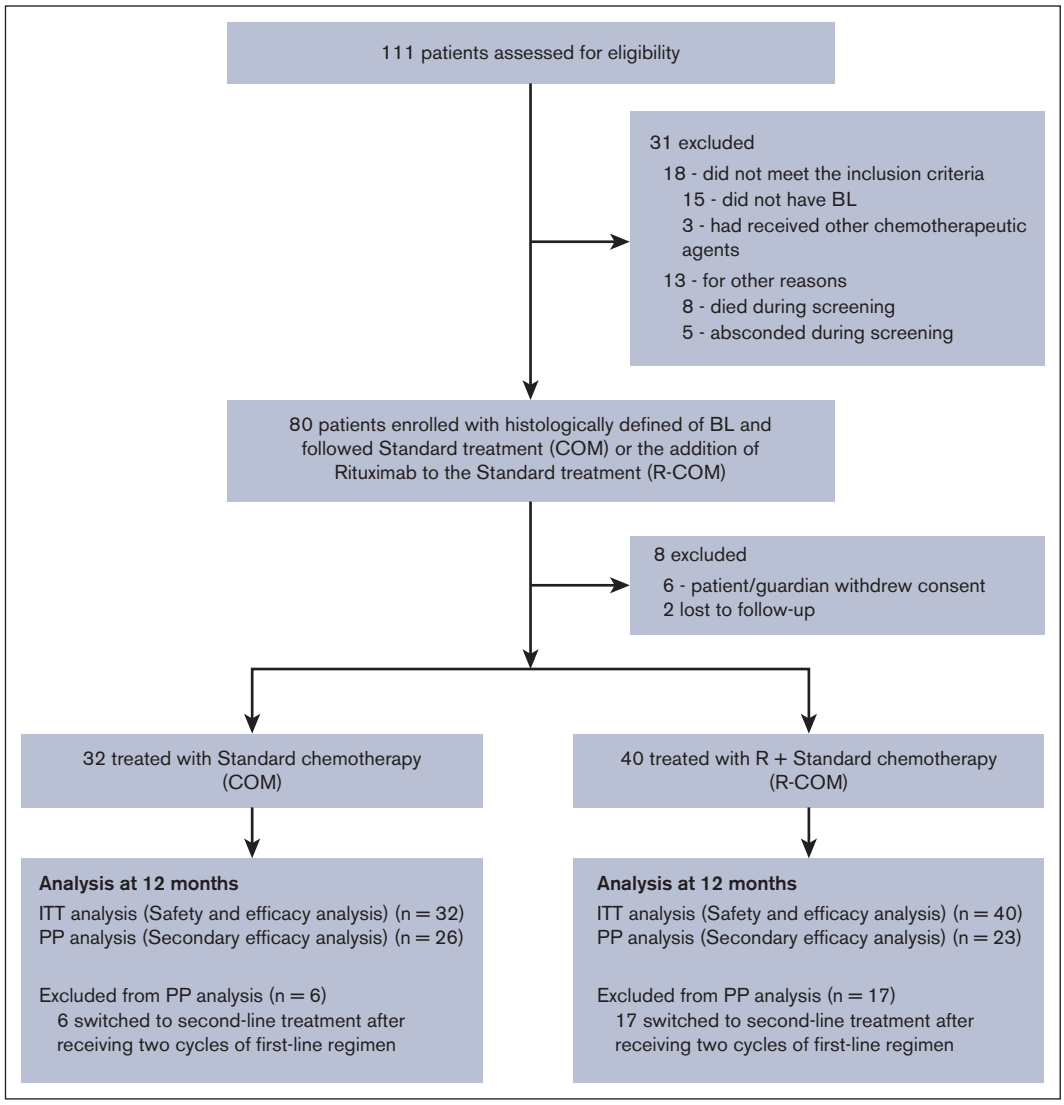

Figure 1. Enrollment, treatment, and follow-up of the patients.

in the R-COM group (6 cycles) than the COM group (3 cycles; $P = .003$), due to more deaths during COM therapy (Tables 2 and 3).

Among all patients, 20 (28%) experienced acute adverse events of all grades. The R-COM arm had a higher incidence of acute adverse events (38%) than the COM arm (16%; $P = .039$). Grade 3 or 4 adverse events were similar: 18% (7 cases) in the R-COM group and 16% (5 cases) in the COM group. Common grade 3 or 4 events included febrile neutropenia,[6] neutropenic sepsis,[6] and oral mucositis.[2] No infusion-related reactions were reported (Table 2).

A total of 4 patients (5.5%) died during treatment. Three deaths occurred in the COM group and 1 in the R-COM group. In the COM group, the first death occurred during the second cycle of COM, attributed to infection and concurrent renal failure. The second death, also due to infection, occurred during the administration of the first cycle of COM. The third death occurred during the second cycle of COM, attributed to infection. In the R-COM group, the single death occurred during the second cycle of second-line chemotherapy (R-IVAC) and was attributed to infection.

Efficacy

The median follow-up was 23 months overall, with a median follow-up of 16 months (IQR, 9.00-26.00) in the R-COM group and 32.00 months (IQR, 26.00-37.00) in the COM group.

EFS at 12 months for the entire ITT population was 67% (95% CI, 53-84) with R-COM and 43% (95% CI, 29-64) with COM (Figure 2A). In the EFS analysis, the hazard ratio (HR) for an event was 0.49 (95% CI, 0.24-0.98; $P = .045$). There were 54 events: 32 in the R-COM group and 22 in the COM group (Table 3).

Interestingly, the R-COM group had higher rates of primary refractory disease (35% vs 13% in the COM group), requiring a switch to second-line therapy after 2 cycles of R-COM.

Table 1. Characteristics of the patients at baseline

Characteristics	Overall, N = 72	Standard chemotherapy (COM), n = 32	R + standard chemotherapy (R-COM), n = 40	*P* value*
Age, median (IQR), y	9.5 (6.8-12.0)	8.5 (6.8-12.3)	10.0 (6.8-12.0)	.9
Sex, n (%)				.8
Female	17 (24)	8 (25)	9 (23)	
Male	55 (76)	24 (75)	31 (78)	
B-symptoms, n (%)	64 (89)	27 (84)	37 (93)	.5
Peripheral LAD, n (%)	30/57 (53)	16/26 (62)	14/31 (45)	.2
Jaw mass, n (%)	29/65 (45)	14/27 (52)	15/38 (39)	.3
Mediastinal mass, n (%)	2/55 (3.6)	2/24 (8.3)	0/31 (0)	.2
Abdominal mass, n (%)	41/60 (68)	13/24 (54)	28/36 (78)	.054
HIV positive, n (%)	2/52 (3.8)	1/23 (4.3)	1/29 (3.4)	>.9
LDH levels, median (IQR), IU/L	997 (678-1594)	961 (795-1477)	1173 (598-1669)	.6
Cytopenias, n (%)	52/71 (73)	22/31 (71)	30/40 (75)	.7
Clinical stage, n (%)				.070
Advanced stage	41 (57)	22 (69)	19 (48)	
Limited stage	31 (43)	10 (3)	21 (53)	

LAD, lymphadenopathy; LDH, lactate dehydrogenase; R, rituximab.
*Pearson χ^2 test; Wilcoxon rank-sum test; Fisher exact test.

Table 2. Treatment course and acute adverse events

Characteristic	Overall, N = 72	Standard chemotherapy (COM), n = 32	R + standard chemotherapy (R-COM), n = 40	*P* value*
First-line treatment duration, median (IQR), wk	14 (7-17)	10 (2-16)	15 (12-17)	.023
Completed first-line cycles, median (IQR), number of cycles	6.00 (2.75-6.00)	3.00 (1.00-6.00)	6.00 (3.75- 6.00)	.003
Interval between first-line cycles, median (IQR), wk	2.00 (1.75- 3.00)	2.00 (1.00- 3·00)	3.00 (2.00-3.00)	.13
Received second-line treatment, n (%)	23 (32)	6 (19)	17 (43)	.032
All adverse events, n	63	17	46	
Patients who experienced adverse events, n (%)	20 (28)	5 (16)	15 (38)	.039
Patients with grade 3/4 adverse events, n (%)	12 (17)	5 (16)	7 (18)	.8
Patients with grade 3/4 hematological adverse events†, n (%)	6 (8.3)	3 (9.4)	3 (7.5)	>.9
Anemia	1 (1.4)	1 (3.1)	0 (5.0)	.4
Neutropenia	6 (8.3)	3 (9.4)	3 (7.5)	>.9
Patients with grade 3/4 nonhematological adverse events†, n (%)	12 (17)	5 (16)	7 (18)	.8
Febrile neutropenia	6 (8.3)	3 (9.4)	3 (7.5)	>.9
Sepsis	6 (8.3)	3 (9.4)	3 (7.5)	>.9
Oral mucositis	2 (2.8)	1 (3.1)	1 (2.5)	>.9
Fever	1 (1.4)	1 (3.1)	0 (0)	.4
Nausea	1 (1.4)	0 (0)	1 (2.5)	>.9
Vomiting	1 (1.4)	0 (0)	1 (2.5)	>.9
Diarrhea	1 (1.4)	0 (0)	1 (2.5)	>.9
Hypotension	1 (1.4)	0 (0)	1 (2.5)	>.9
Acute kidney injury	1 (1.4)	1 (3.1)	0 (0)	>.9
Infusion-related reactions	0 (0.0)	0 (0.0)	0 (0)	

*Wilcoxon rank sum test; Pearson χ^2 test; Fisher exact test.
†The total number of patients is less than the total number of grade 3 or 4 adverse events, because some patients experienced multiple events.

Table 3. Number and type of events and number of deaths of the entire ITT population

Characteristic	Overall, N = 72	Standard chemotherapy (COM), n = 32	R + standard chemotherapy (R-COM), n = 40
Primary refractory disease, n (%)	18 (25)	4 (13)	14 (35)
Relapse or progressive disease, n (%)	12 (17)	2 (6.3)	10 (25)
Second cancer, n (%)	0 (0)	0 (0)	0 (0)
Death, treatment related, n (%)	4 (5.5)	3 (9.4)	1 (2.5)
Death, disease related, n (%)	20 (27.8)	13 (40.6)	7 (17.5)
Total no. of events	54	22	32
Total no. of deaths	24	16	8

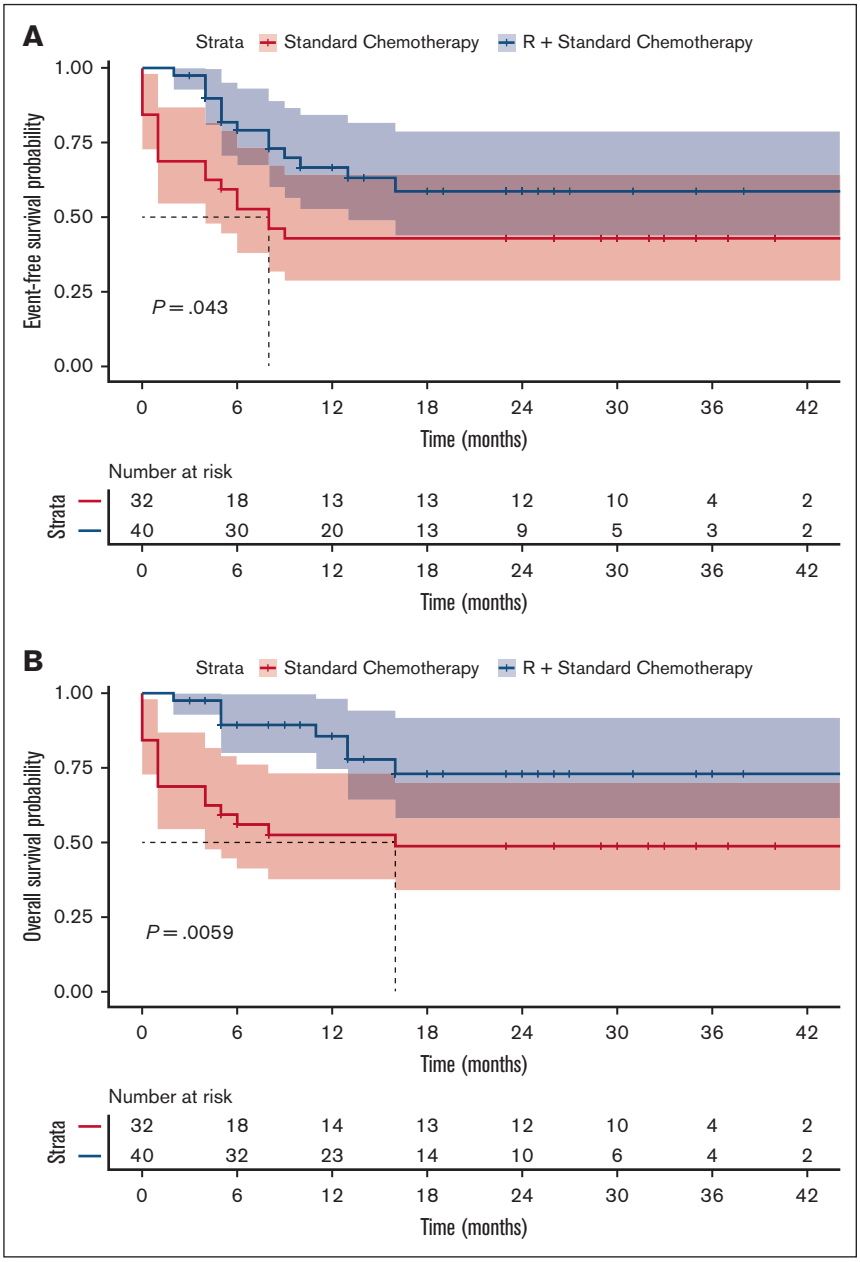

Figure 2. EFS and OS for the entire ITT cohort, according to treatment group. Kaplan-Meier projections for EFS (A), defined as freedom from primary refractory disease, initial onset of progression, relapse after a response, death from any cause, or the development of a second cancer; and OS (B), defined as freedom of death from any cause. The shaded area illustrates the 95% CIs.

The reduction in mortality in the R-COM arm was notable, with fewer disease-related deaths (17.5% in R-COM vs 40.6% in COM) and treatment-related deaths (2.5% in R-COM vs 9.4% in COM). This suggests that rituximab might mitigate the risk of death, even in patients who eventually progress or relapse.

Twelve-month OS for the entire ITT population was 86% (95% CI, 75-98) in the R-COM group and 53% (95% CI, 38-73) in the COM group (HR, 0.32; 95% CI, 0.14-0.75; $P = .009$; Figure 2B).

Of the 72 patients in the COM and R-COM arms, 23 (31.9%) were switched to second-line treatment after receiving 2 cycles of the first-line regimen, according to protocol. In a secondary efficacy analysis, we evaluated those who completed at least 6 cycles of COM or R-COM without switching to second-line therapy (PP analysis). In this PP population, the 12-month OS rate was 100% (95% CI, 100-100) in the R-COM group and 49% (95% CI, 33-73) in the COM group (HR, 0.07; 95% CI, 0.01-0.51; $P = .009$; supplemental Table 1; supplemental Figure 2).

Interestingly, although there was a trend toward worse outcomes for all children with advanced-stage disease in the ITT population and those initially treated with COM, this was overcome by the addition of rituximab (supplemental Figures 3-5).

Sensitivity analysis

To account for the 2 patients lost to follow-up, a sensitivity analysis was performed. In the first scenario, in which the patients were censored at their last follow-up, the 12-month OS for the ITT population was 86% (95% CI, 75-98) in the R-COM group and 53% (95% CI, 38-74) in the COM group (HR, 0.32; 95% CI, 0.14-0.75; $P = .009$). In the second scenario, in which the patients were included as events (assuming death), the 12-month OS was 83% (95% CI, 71-97) in the R-COM group and 51% (95% CI, 36-71) in the COM group (HR, 0.33; 95% CI, 0.15-0.75; $P = .008$; supplemental Figure 6; supplemental Tables 2 and 3).

These results confirm that the exclusion or inclusion of the 2 patients does not materially affect the study's conclusions, because the survival benefit of the R-COM regimen remains robust under both scenarios.

Discussion

To our knowledge, this study is the first to use continuous monitoring and grading of toxicity events based on Common Terminology Criteria for Adverse Events criteria for the less-intensive INCTR protocol COM that is used to treat BL in equatorial SSA. Furthermore, this prospective, nonrandomized observational study demonstrates that the addition of 6 cycles of rituximab to this INCTR protocol is feasible and results in significant survival benefits while maintaining a manageable safety profile.

The safety profile of R-COM was comparable with COM alone, with no significant differences in the incidence of grade ≥3 toxicities. However, the higher incidence of acute adverse events, primarily neutropenia and infections, in the R-COM group highlights the need for enhanced supportive care measures. No instances of rituximab infusion–related hypersensitivity reactions were observed in patients in the R-COM group. This aligns with findings from a safety rituximab trial in adults with diffuse large B-cell lymphoma in Malawi, in which only 1 patient experienced a rituximab infusion–related hypersensitivity reaction.[23]

Treatment-related mortality, primarily due to infections, underscores the critical importance of addressing infection prevention and management to maximize the benefits of rituximab in these settings. Importantly, no deaths were directly attributed to rituximab, supporting its feasibility and safety in resource-limited contexts.

Comparatively, reports from intensive treatment protocols used in high-income countries for BL treatment show a relatively higher incidence of adverse events of all grades (>90%).[5,12-15] However, even in these settings, rituximab does not significantly increase toxicity compared with chemotherapy alone.[5] The lower incidence of adverse events in our INCTR protocol–based regimen reflects its less-intensive design, adapted to address SSA's limited supportive care infrastructure.

The challenges associated with high-intensity regimens in SSA are well documented.[8-10] Studies of BL in Malawi report suboptimal outcomes, with 1-year EFS rates <40% for advanced disease treated with anthracycline-based regimens, as well as poor OS due to advanced presentations and limited supportive care.[9,10] Additionally, Ozuah et al highlight stagnant BL survival rates of 30% to 50% over decades in SSA.[11] These findings reinforce the need for pragmatic approaches, such as adding rituximab to the low-intensity INCTR protocol, to improve outcomes while awaiting the development of supportive care infrastructure for high-intensity regimens.

The 12-month OS and EFS were significantly higher in the R-COM group than the COM group, with an HR favoring R-COM for both outcomes. Sensitivity analysis confirmed that these survival benefits remained robust, even when accounting for missing data.

The observed survival benefit was particularly pronounced in patients with advanced-stage disease, a critical predictor of poor outcomes. Although the proportion of patients with advanced-stage disease was higher in the COM group than in the R-COM group (69% vs 48%), stratified analyses revealed that rituximab helped overcome this disparity, significantly improving outcomes even in advanced-stage patients. These findings underscore the potential of R-COM as a valuable treatment option in resource-limited settings, in which advanced-stage presentations are common due to late diagnosis.

Rituximab has shown significant clinical activity in children with aggressive high-grade Non-Hodgkin Lymphoma (NHL), including EBV-negative BL.[5] However, there is increasing evidence that the biology of EBV-positive and EBV-negative BL might differ. Studies have highlighted different mutation and methylation profiles and differences in protein profiles, such as the overexpression of enolase 1 and heat shock protein 90B1 in endemic BL and proliferating cell nuclear antigen in sporadic BL.[24,25] These findings justify studying the impact of rituximab in EBV-positive endemic BL, because treatment outcomes and biological drivers in endemic BL may differ significantly from those of sporadic BL in high-income settings. This distinction emphasizes the need for tailored approaches in resource-limited contexts such as SSA.

As with any nonrandomized observational study, this study has inherent limitations, including susceptibility to confounding. However, we think that this design is uniquely suitable for studying feasibility and safety of agents already approved outside of SSA, where historical standard of care control cohorts are often lacking,

and therefore, the results of a single-arm phase 2 design are difficult to interpret. Future studies, potentially incorporating pragmatic randomized designs, are warranted to confirm these findings and better delineate rituximab's independent impact.

In addition to safety and efficacy, a further essential consideration for any new intervention is cost-effectiveness, given that health systems face many competing demands and need to decide how to allocate their limited resources. In resource-rich settings, adding rituximab to lymphoma treatment is considered cost-effective.[26] Evidence from SSA is limited; however, a study in diffuse large B-cell lymphoma in Malawi found that adding rituximab to current treatment gave a cost per Disability-Adjusted Life Year (DALY) averted slightly above the gross domestic product (GDP)-based cost-effectiveness threshold.[27] In our study, adding rituximab to 6 cycles of COM increased the chemotherapy cost by $1800 per patient (drug cost alone), at the price at which rituximab was provided for the study. A rigorous economic evaluation is needed, taking into account all changes in costs and outcomes, to gain a full understanding of the cost-effectiveness of adding rituximab to COM in this setting.

In summary, our study shows that R-COM is a feasible and safe first-line treatment option for patients with BL in equatorial SSA, yielding improved OS. These findings are particularly important given the limited resources and infrastructure available for implementing intensive treatment regimens in this setting.

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Authorship

Contributions: W.F.M., L.C., H.M., and A.S. contributed to the conception and design of the study; H.M., P.M.A., S.M., G.S., I.O., H.N., P.N., P.G.L., J.P.K., I.D.L., C.A., E.M., and K.S. participated in data collection and analysis; W.F.M. wrote the first draft of the manuscript; W.F.M., L.M., D.V., L.C., and A.S. reviewed the manuscript critically; and all authors read and approved the final manuscript.

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ORCID profiles: W.F.M., 0000-0002-0016-7551; I.O., 0000-0001-8000-9483; I.D.L., 0000-0002-6118-542X; M.D.O., 0000-0002-4178-2809; P.M.A., 0009-0001-1979-8396; G.S., 0000-0001-9068-0991; H.M., 0009-0007-6501-535X; E.M., 0000-0001-5938-5628; K.S., 0000-0002-6433-6174; C.C., 0000-0001-5154-7872; D.V., 0000-0002-3984-1507; L.M., 0000-0001-6382-1795; A.S., 0000-0002-3938-8490.

Correspondence: William Frank Mawalla, Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Science, PO Box 65001, Upanga, Dar es Salaam, Tanzania; email: mawallawf@ymail.com.

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