Safety and efficacy of rituximab in patients with diffuse large B-cell lymphoma in Malawi: a prospective, single-arm, non-randomised phase 1/2 clinical trial

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Summary

Background—There are no clinical trials involving patients with diffuse large B-cell lymphoma (DLBCL) in sub-Saharan Africa since antiretroviral therapy (ART) for HIV became widely available in this region. We aimed to establish the safety and efficacy of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with DLBCL in Malawi.

Methods—This prospective, single-arm, non-randomised phase 1/2 clinical trial was done at Kamuzu Central Hospital Cancer Clinic (Lilongwe, Malawi). Eligible patients were adults (aged 18–60 years) with newly diagnosed DLBCL, an Eastern Cooperative Oncology Group performance status of 0–2, a CD4 count of 100 cells per μL or higher (if HIV-positive), measurable disease by physical examination, an absolute neutrophil count of 1000×10^9 cells per L or higher, a platelet count of 100×10^9 platelets per L or higher, a serum creatinine concentration of 132·60 μmol/L or less, a total bilirubin concentration of 34·21 μmol/L or less, a negative urine pregnancy test in women of childbearing potential, and no previous cytotoxic therapy. Pregnant or breastfeeding women, and individuals with CNS involvement from DLBCL, chronic hepatitis B infection (unless they were receiving tenofovir plus lamivudine), or any other comorbidities that would compromise the protocol objectives were excluded. Eligible patients received intravenous rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1·4 mg/m^2 (maximum 2 mg/m^2), and oral prednisone 100 mg or an equivalent drug every 21 days for up to six cycles. HIV-positive patients received concurrent ART. The primary outcome was the proportion of patients with National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or 4 non-haematological toxic effects or treatment-related deaths after six cycles of treatment. Secondary efficacy outcomes included the proportion of patients with a complete response after six cycles of treatment, and progression-free survival and overall survival at 12 months and 24 months. This trial is registered with ClinicalTrials.gov, NCT02660710.

Findings—Between Aug 1, 2016, and July 31, 2019, 76 patients were screened, of whom 37 were eligible for the study and received R-CHOP. The median age of patients was 44 years (IQR 39–49) and 16 (43%) were women. Of all 37 patients, 20 (54%) had stage III or IV DLBCL, and the age-adjusted international prognostic index was 2 or higher in 25 (68%) patients. 27 (73%) patients were HIV-positive, with a median CD4 count of 208 cells per μL (IQR 144–422), and 21 (78%) patients were receiving ART at enrolment. Patients completed a median of six cycles (IQR 4–6). Grade 3 or 4 non-haematological toxic effects were reported in 12 (32% [95% CI 19–49])

patients, the most common of which was infection (nine [24%] patients). Of 16 (43%) deaths, ten were due to progression of DLBCL, four were due to treatment-related complications, and two were due to other causes, yielding a treatment-related mortality of 11% (95% CI 4–26%). Grade 3 or 4 neutropenia was observed in 26 (70%) patients, and grade 3 or 4 anaemia was observed in 11 (29%) patients. A total of 22 (59%) patients had a complete response. Overall survival was 68% (95% CI 50–80) at 12 months and 55% (37–70) at 24 months, and progression-free survival was 59% (42–73) at 12 months and 53% (35–68) at 24 months.

Interpretation—R-CHOP could be feasible, safe, and efficacious in patients with DLBCL in Malawi. This is the first completed clinical trial on DLBCL focused on sub-Saharan African populations. Given the paucity of data on treatment of DLBCL from this region, these results could inform emerging cancer treatment programmes in sub-Saharan Africa.

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Introduction

The incidence of non-Hodgkin lymphoma is increasing in sub-Saharan Africa, where approximately 50000 new cases were diagnosed in 2019.[1] The prevalence of HIV infection in patients with non-Hodgkin lymphoma in this region ranges from 30% to 60%.[2,3] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma worldwide.[4] Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the international first-line standard-of-care that cures most patients.[4] DLBCL is highly associated with HIV infection,[5,6] and is a common, curable lymphoma throughout sub-Saharan Africa, where the global HIV epidemic is concentrated.[7,8]

Adding rituximab to CHOP has been the primary therapeutic advance for DLBCL in the past two decades, yielding absolute increases in long-term overall survival of 10–20% compared with CHOP alone,[4,9,10] and rituximab was approved by the US Food and Drug Administration in 1997. Rituximab also improves outcomes in patients with HIV-associated DLBCL, although this benefit in resource-rich settings is less clear in patients with CD4 cell counts of less than 50 per μL (ie, those with severe immunosuppression) compared with patients who have higher CD4 cell counts due to the increased risk of treatment-related infectious complications.[11]

Rituximab is currently included in the WHO Model List of Essential Medicines, and several biosimilar drugs, with equivalent pharmacokinetic, safety, and efficacy data to the proprietary drug, are commercially available worldwide.[12,13] Despite the importance and availability of biosimilar drugs, rituximab remains unavailable in most public sector settings in sub-Saharan Africa because of cost. Additionally, there are no prospective data for rituximab focused on populations in sub-Saharan Africa, where HIV is prevalent, the supportive care infrastructure is weak, haematopoietic growth factors are often unavailable, and the burden of opportunistic infections is high.[14] Robust safety, efficacy, and cost-effectiveness data from this region are essential to inform the programmatic implementation of rituximab, and to convince policy makers facing many competing priorities that newer anti-cancer drugs, such as rituximab, can be prudent public health investments.

To address these gaps, we did a clinical trial of the Indian rituximab biosimilar Reditux (Dr Reddy's Laboratories, Hyderabad, Telangana, India) plus CHOP in Malawi, a low-income country in sub-Saharan Africa with a gross domestic product of US$411 per person, an annual health expenditure of $38 per person, a human development index rank of 172 of 189 countries, and where the prevalence of HIV is 9%.[15–17] We aimed to investigate the safety and efficacy of R-CHOP in HIV-infected and HIV-uninfected patients with DLBCL. We hypothesised that rituximab would be safe and effective for patients with DLBCL, even under routine programmatic conditions.

Methods

Study design and patients

This prospective, single-arm, non-randomised phase 1/2 clinical trial was done at the Kamuzu Central Hospital Cancer Clinic in Lilongwe, Malawi.

Eligible patients were adults (aged 18–60 years) with newly diagnosed DLBCL, an Eastern Cooperative Oncology Group performance status of 0–2, a CD4 count of 100 cells per μL or higher (if HIV-positive), measurable disease by physical examination, an absolute neutrophil count of 1000×10^9 cells per L or higher, a platelet count of 100×10^9 per L or higher, a serum creatinine concentration of 132·60 μmol/L or less, a total bilirubin concentration of 34·21 μmol/L or less, a negative urine pregnancy test in women of childbearing potential, and no previous cytotoxic therapy. Pregnant or breastfeeding women, and individuals with CNS involvement from DLBCL on clinical assessment or by cerebrospinal fluid cytology, chronic hepatitis B infection (unless they were receiving tenofovir plus lamivudine), or any other comorbidities (including cardiac disease) that would compromise the protocol objectives were excluded. For diagnosis of DLBCL, biopsy specimens were evaluated on-site in Lilongwe in real-time by immunohistochemistry and telepathology, with consensus review by 2–4 pathologists in the USA (NDM and YF) and in Malawi (TT and MM). Biopsy tissue specimens from all patients were then transported to the University of North Carolina (Chapel Hill, NC, USA) for delayed repeat immunohistochemical staining and review (by AL and CR).[18,19] Baseline staging evaluations were done as described in the appendix (pp 32–33).

All patients provided written informed consent. The study was approved by the institutional review board at the University of North Carolina at Chapel Hill (Chapel Hill, NC, USA), and the National Health Sciences Research Committee and Pharmacy, Medicines, and Poisons Board (Lilongwe, Malawi).

Procedures

Eligible patients received intravenous rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² (maximum 2 mg/m²), and oral prednisone 100 mg or an equivalent drug every 21 days for up to six cycles. Dosing was modelled on the R-CHOP group of the phase 3 Intergroup Trial Alliance/CALGB 50303 study.[20] Treatment was administered at the Kamuzu Central Hospital Cancer Clinic and as described in the appendix (pp 9–12). Allopurinol 300 mg twice daily was administered on days

1–5 of cycle one. Haematopoietic growth factors were not routinely available in Malawi during the study period. Between the screening visit and R-CHOP initiation, patients could receive up to 10 days of pre-phase corticosteroids but no cytotoxic treatment. Patients were assessed before treatment; at each treatment visit (ie, every 21 days); and then every 3 months until 24 months after treatment. Assessments by clinicians included clinical history, details of treatment and adverse effects, performance status, and results of blood counts and other relevant tests. Imaging with chest x-ray and abdominal ultrasound were done at baseline and at the end of treatment. A bone marrow biopsy was done at baseline for all patients, but was only repeated at the end of treatment if lymphomatous involvement was present at baseline. Lumbar puncture at baseline was done only in high-risk patients (ie, those with lymphoma, with involvement of two or more extranodal sites and elevated lactate dehydrogenase concentrations, or bone marrow, testicular, epidural, ocular, breast, or paranasal sinus involvement). Lumbar puncture was repeated as clinically indicated (see appendix p 10). In the event of clinical suspicion of relapse, additional evaluation was done as clinically indicated.

Protocol-defined dose adjustments and delays for non-haematological and haematological toxicities are described in the appendix (pp 13–16).

HIV-infected patients received oral co-trimoxazole 960 mg once daily, consistent with Malawi guidelines, plus oral ciprofloxacin 500 mg twice daily during days 8–15 of each chemotherapy cycle, and oral fluconazole 100 mg once daily continuously throughout chemotherapy until recovery of absolute neutrophil counts of 500×10^9 cells per L or higher after treatment completion. HIV-uninfected patients received oral ciprofloxacin 500 mg twice daily during days 8–15 of each chemotherapy cycle if febrile neutropenia (ie, a neutrophil count of $<1\times10^9$ cells per L) developed after a previous chemotherapy cycle. For HIV-infected patients, concurrent antiretroviral therapy (ART) was administered to all patients consistent with Malawi guidelines. These guidelines evolved over the study period in accordance with WHO recommendations, with tenofovir, lamivudine, and efavirenz changed to tenofovir, lamivudine, and dolutegravir as the recommended first-line ART for most patients. For patients receiving ritonavir, the dose of vincristine was reduced by 50% with each cycle. Consolidative radiotherapy after R-CHOP was not available in Malawi during the study period for persistent or bulky disease. Patients received transportation reimbursement for all visits, as per Malawi National Health Sciences Research Committee guidelines.

Outcomes

The primary outcome was the proportion of patients with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 grade 3 or 4 non-haematological toxic effects or treatment-related deaths after six cycles of treatment. Assigning cause of death in Malawi is often difficult given limited diagnostic capabilities, and some deaths could have occurred outside of health facilities. Therefore, two senior non-study Malawian clinicians were enlisted to review all study data for deceased patients and assign cause of death as probably treatment-related, lymphoma-related, related to another cause, or indeterminable. In the event of discordant conclusions, a third senior clinician made the final decision.

Deaths occurring outside Kamuzu Central Hospital Cancer Clinic were adjudicated as related or unrelated to treatment on the basis of known clinical information, including DLBCL status at the time of death, proximity to treatment, a family interview, and review of the most recent cancer clinic records, laboratory data, imaging data, and medical records from peripheral health centres.

The secondary outcomes were the proportion of patients with grade 3 or 4 non-haematological toxic effects after six cycles of treatment according to HIV status; the dose intensity of R-CHOP in patients with and without HIV infection; treatment efficacy, as assessed by progression-free survival and overall survival at 12 months and 24 months after treatment, and the proportion of patients with a complete response after six cycles, overall and according to HIV status; health-related quality of life, as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, overall and according to HIV status; and the cost-effectiveness of R-CHOP administered for six cycles, modelled by use of locally derived clinical trial and cost data. Response was assessed by investigators according to standard international criteria by physical examination, chest radiography, abdominal sonography, and in rare instances CT scan. PET was not available in Malawi during the study period. Progression-free survival was defined as the time from treatment initiation until disease progression or death. Overall survival was defined as the time from treatment initiation until death. A complete response was defined as the disappearance of all evident disease (additional details about treatment response assessments are described in the appendix [pp 32–34]).

Post-hoc exploratory endpoints included the frequency of treatment delays (defined as an interval of 7 days or more between cycles) and the proportion of patients with grade 3 or 4 haematological toxic effects after six cycles of treatment, according to HIV status.

Statistical analysis

Given the single-arm design of this phase 1/2 study, a sample size of at least 36 patients was calculated on the basis of desired precision of the safety estimates for grade 3 or 4 non-haematological toxicity (maximum allowable 95% CI width of 34%) and treatment-related deaths (maximum allowable 95% CI width of 30%). Primary and safety analyses were done in all patients with measurable disease who had received at least one cycle of R-CHOP.

In prespecified exploratory post-hoc analyses, differences between HIV-infected and HIV-uninfected patients were assessed with an exact Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. All reported p values are two-sided and presented without adjustment for multiple comparisons. Progression-free survival and overall survival were estimated by use of Kaplan-Meier methods, and the log-rank test was used to assess differences between HIV-infected and HIV-uninfected individuals.

Study data were monitored by the University of North Carolina Lineberger Comprehensive Cancer Center Data and Safety Monitoring Committee. Statistical analyses were done with Stata, version 6.1.

This trial is registered with ClinicalTrials.gov, NCT02660710.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 1, 2016, and July 31, 2019, 76 patients were screened for eligibility (figure 1). The primary reasons for exclusion were non-DLBCL diagnosis (n=17) and having a CD4 count of less than 100 cells per μL (n=11). Of 59 patients with confirmed DLBCL who had completed screening, 39 (66%) were enrolled and received R-CHOP. Of these patients, one (3%) was subsequently diagnosed with Burkitt lymphoma and one (3%) was subsequently diagnosed with follicular lymphoma after pathological review of biopsy specimens in the USA. As such, 37 patients were included in the final analyses. No patients had transformed DLBCL. The median time from screening to initiation of R-CHOP was 10 days (range 2–30).

Characteristics of the 37 patients with DLBCL who received R-CHOP are shown in table 1. The median age of patients was 44 years (IQR 39–49), and 16 (43%) were women. 20 (54%) patients had stage III or IV disease, 15 (41%) had palpable masses of 10 cm or more in diameter, the median lactate dehydrogenase concentration was 515 IU/L (IQR 373–692; the laboratory upper limit of normal was defined as 250 IU/L), and 25 (68%) patients had an age-adjusted absolute International Prognostic Index of 2 or higher. The median tumour Ki-67 expression score was 80% (IQR 60–90). Epstein-Barr virus (EBV) status, as assessed by EBV-encoded RNA in-situ hybridisation and immunophenotype classification by immunohistochemistry with the Hans classifier,[21] was known for 28 (76%) patients. Of these patients, two (7%) were EBV-positive and 16 (57%) had a germinal centre B-cell phenotype. Of all 37 patients, 27 (73%) were HIV-positive, 21 (78%) of whom were receiving ART for 3 months or more before they were diagnosed with DLBCL. Among the 27 HIV-positive patients, the median duration of ART was 36 months (IQR 5–86), the median CD4 count was 208 cells per μL (144–422), and 20 (74%) patients had viral suppression (defined as HIV RNA concentrations of <1000 copies per mL). Baseline characteristics did not differ substantially between HIV-positive and HIV-negative patients.

The treatment course and proportion of patients with grade 3 or 4 toxic effects are shown in table 2. As of Aug 14, 2020, all patients had completed a median of 6 cycles (IQR 4–6) of R-CHOP. A total of 12 (32% [95% CI 19–49]) patients had grade 3 or 4 non-haematological toxic effects (table 2). The most frequent grade 3 or 4 non-haematological toxic effects were infections (nine [24%] patients), including *Escherichia coli* bacteraemia (n=2), skin and soft tissue infections (n=2), malaria (n=1), *Proteus mirabilis* osteomyelitis (n=1), *Streptococcus pneumoniae* septic arthritis (n=1), *Staphylococcus aureus* empyema (n=1), and progressive multifocal leukoencephalopathy (n=1). Progressive multifocal leukoencephalopathy associated with John Cunningham virus reactivation occurred in the context of patient nonadherence to ART, and a decline in the CD4 cell count from 145 cells per μL at enrolment to 69 cells per μL at 6 months. After ART was resumed, this patient improved despite persistent neurological impairment. During the initial rituximab infusion, one patient had grade 3 hypersensitivity that resolved with standard measures and did not

recur with subsequent R-CHOP cycles. Of note, grade 3 or 4 non-haematological toxic effects in five (42%) of 12 patients were partly attributable to anatomical complications caused by specific sites of bulky disease. These anatomical complications of DLBCL included gram-negative bacteraemia, which was likely to have occurred due to an anal mass with a suspected fistula, intestinal obstruction due to primary intestinal involvement, soft-tissue superinfection of an ulcerated axillary mass, osteomyelitis in a primary bone DLBCL resulting in a non-healing sinus tract, and empyema due to pathologically confirmed pleural involvement of DLBCL.

Disease and vital status were known for all patients, with a median follow-up of 27 months (IQR 19–34). Of 16 total deaths in the study population, ten were due to DLBCL progression, four were due to treatment-related complications, and two were due to other causes, yielding a treatment-related mortality of 11% (95% CI 4–26). Two deaths from treatment-related complications were due to chronic osteomyelitis leading to progressive renal failure and *S aureus* empyema. Two deaths attributed to treatment-related complications were temporally associated with receipt of treatment, but confirmation of these deaths as treatment-related was not possible, as they occurred at rural health facilities with an inadequate diagnostic infrastructure, such as specialised clinicians, laboratory tests, or imaging. Two deaths from other causes were due to complications of uncontrolled diabetes in patients who responded to R-CHOP, without an alternative infectious or other cause of death identified.

HIV-positive patients had a lower treatment intensity than HIV-negative patients, as reflected by the lower number of treatment cycles, higher frequency of treatment delays, and higher frequency of dose reductions due to the greater severity and duration of neutropenia (table 2). Irrespective of differences in treatment intensity, no significant difference was observed in the overall frequency of grade 3 or 4 neutropenia between HIV-positive and HIV-negative patients. Grade 3 or 4 neutropenia occurred in 26 (70%) of 37 patients overall, and 11 (29%) patients had grade 3 or 4 anaemia. No patients had grade 3 or 4 thrombocytopenia.

Of all 37 patients, 22 (59%) had a protocol-defined complete response. Three additional patients had a protocol-defined partial response with small residual masses, and these patients survived without disease progression for 34 months, 36 months, and 40 months from R-CHOP initiation, suggesting a functional complete response in 25 (68%) patients overall; however, a metabolic complete response could not be confirmed by PET scan in these three patients. Progression-free survival and overall survival in the total cohort are shown in figure 2. Progression-free survival was 59% (95% CI 42–73) at 12 months and 53% (35–68) at 24 months. Overall survival was 68% (50–80) at 12 months and 55% (37–70) at 24 months. No significant differences in progression-free survival (log-rank p=0·43) and overall survival (log-rank p=0·27) according to HIV status were observed.

Discussion

To our knowledge, this is the first clinical trial of rituximab for DLBCL focused on sub-Saharan African populations, and the first clinical trial of the treatment of adults with lymphoma in this region in the current era of widespread access to HIV treatment.[22] We

enrolled patients with DLBCL who had adverse disease characteristics that typically confer poor outcomes (27 [73%] of 37 patients were HIV-positive, 20 [54%] had stage III or IV disease, 15 [41%] had a bulky palpable mass, 25 [68%] had an age-adjusted absolute International Prognostic Index of 2, and median lactate dehydrogenase concentrations were more than two times the upper limit of normal). However, relative to cohorts in high-income countries, patients were likely to have been understaged due to absent PET and restricted CT availability in Malawi. No patients were lost to follow-up, and overall survival at 24 months was 55% (95% CI 37–70) under routine programmatic conditions, which is among the best reported outcomes to date in a sub-Saharan African population. We enrolled 39 (66%) of 59 screened patients who presented to the cancer clinic at the national teaching hospital, and who were confirmed to have DLBCL on-site during the study period. We acknowledge that some referral and selection bias might have occurred, given the extreme centralisation of cancer services and multiple barriers patients face in accessing care in Malawi. R-CHOP was initiated a median of 10 days after the initial screening visit. As a reference, 2-year overall survival in patients with HIV-associated DLBCL receiving R-CHOP or infusions of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin have typically been 60–70%, according to clinical trials done in the USA and Europe.[11,23] Additionally, in the USA, long diagnosis-to-treatment intervals of more than 14 days have been independently associated with improved outcomes in patients with DLBCL compared with shorter intervals (ie, 14 days).[24] These long intervals have been proposed as a reason for better than anticipated outcomes in the control groups of contemporary DLBCL clinical trials, particularly when treatment assignment has required molecular characterisation of tumours.[25]

A 2020 review by the AIDS Malignancy Consortium, which includes leaders of African clinical trial sites involved in the consortium, found no clinical trials actively enrolling patients with HIV-associated lymphoma in sub-Saharan Africa.[26] Additionally, a randomised clinical trial by the same consortium initiated in November, 2016, which aimed to compare an investigational oral regimen with CHOP in patients with HIV-associated DLBCL, was stopped after only seven patients in four sub-Saharan African countries (including Malawi) were enrolled over 2 years.[26,27] Before this trial, the only completed clinical trial focused on adults with lymphoma in sub-Saharan Africa evaluated an investigational oral regimen (lomustine, etoposide, cyclophosphamide, and procarbazine) in HIV-infected patients in Kenya and Uganda in 2001–05, before public sector ART was widely available.[22] Of 149 screened patients with HIV and lymphoma, 49 (33%) were ultimately given the investigational regimen, among whom median overall survival was 12·3 months. In this previous trial, patients with diverse non-Hodgkin lymphoma histologies were included, with only seven patients having confirmed DLBCL. Therefore, given the extreme paucity of high-grade contemporary clinical trial data from the assessment of a contemporary international standard of care regimen in sub-Saharan Africa, together with the increasing incidence of HIV-associated non-Hodgkin lymphoma throughout the region,[6,28,29] our findings can inform emerging efforts to address gaps in cancer treatment. Despite the limitations of our study, including the small sample size, the absence of a control group, and the single-centre design, our data could be informative. For comparison, in a recent report published in 2019, 2-year overall survival was 42% (95% CI 30–53)

in an unselected historical cohort of patients (outside a clinical trial) with DLBCL in Malawi who received CHOP without rituximab under similar programmatic conditions to this trial in 2013–17.[7] An additional limitation of this study was that quality-of-life data were not collected with sufficient rigour nor completeness. Efforts are underway to translate and validate patient-reported outcome instruments to better capture quality- of-life data in Malawi for future studies.

We also note the occurrence of frequent grade 3 or 4 toxic effects among patients in our study, including neutropenia (26 [70%] of 37 patients), anaemia (11 [30%]), and infection (nine [24%]). Neutropenia was generally manageable with protocol-specified dose reduction and treatment delay, even in the absence of available routine haematopoietic growth factor during the study period. Recent increases in the availability of haematopoietic growth factor in many sub-Saharan African settings in the past 12 months could help mitigate risk of neutropenia and increase the achievable cumulative dose and dose intensity of R-CHOP in patients with DLBCL. Most treatment-related infectious complications were successfully identified and managed in our study; however, this detection required adverse event monitoring and laboratory diagnostic capacity, which might not be present in many routine programmatic settings across the region. Although increasing haematopoietic growth factor availability in sub-Saharan Africa can help mitigate the risk of infection in future studies, we also excluded patients with a CD4 count of less than 100 cells per μL because of safety concerns for severely immunosuppressed patients, and we mandated concurrent ART in all HIV-infected patients. Therefore, our findings should not be generalised to HIV-positive patients with DLBCL who do not receive concurrent ART or who have low CD4 counts. Treatment-related mortality in our study was 11% (95% CI 4–26), compared with 18% in the unselected historical cohort of patients with DLBCL in Malawi who received CHOP without rituximab in 2013–17 under similar programmatic conditions.[7] Of note, two deaths in our study occurred due to uncontrolled diabetes in patients who had a complete response to R-CHOP, without an alternative infectious or other cause of death identified. These outcomes highlight the major challenges we encountered in treating cancer patients with comorbidities other than HIV in Malawi. Robust programmes in sub-Saharan Africa for chronic diseases other than HIV are generally scarce. We diagnosed two patients with new uncontrolled diabetes, one during enrolment and one at R-CHOP initiation, but we did not have the specialised capacity to provide intensive inpatient blood glucose management, as these services were not routinely available in the Malawi public sector.

In conclusion, R-CHOP could be a feasible treatment option for patients with DLBCL under routine programmatic conditions in Malawi, with a favourable safety and efficacy profile relative to scant existing regional literature. Given the paucity of similar data from this region, our results could inform emerging cancer treatment programmes and priorities in sub-Saharan Africa. Opportunities to participate in oncology clinical trials are scarce throughout the region, which is rightly viewed as an issue of cancer health equity, even if high quality observational data can also inform cancer care policies and practice.[30] Large randomised multicentre studies to rigorously test treatments for DLBCL in sub-Saharan Africa are needed, and should include studies evaluating subcutaneous rituximab administration with various chemotherapy platforms and individualised risk-adapted and response-guided strategies to better guide treatment intensification or de-intensification.

Finally, in addition to rigorous safety and efficacy evaluation, formal cost-effectiveness analyses of rituximab and other novel drugs in sub-Saharan Africa will be important to provide a strong case for investment to governments and policy makers when they allocate limited resources and consider providing new cancer treatments to the populations they serve.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data sharing

Deidentified individual participant data underlying the reported results will be available with publication of this study. Only approved study proposals with a signed data access agreement will be granted access to these data. A copy of the study protocol is available in the appendix. For all requests, please contact satish.gopal@nih.gov.

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Research in context

Evidence before this study

We searched PubMed, Embase, and Global Health biomedical research databases on Dec 1, 2020, using the search terms "lymphoma", "non-hodgkin lymphoma", "diffuse large B-cell lymphoma", "outcomes", "survival", "treatment", "HIV", "chemotherapy", "rituximab plus chemotherapy", "CHOP", and "R-CHOP". We searched for prospective treatment trials for diffuse large B-cell lymphoma (DLBCL) published in English between Jan 1, 1990, and Nov 30, 2020. Non-English articles were included when an English translation of the abstract was available. We also reviewed references from relevant articles to identify studies that might have been missed by the aforementioned search terms. We found that the integration of rituximab (R) to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the primary therapeutic advance for DLBCL in high-income countries in the past two decades, yielding absolute increases in long-term overall survival of 10–20% compared with CHOP alone. Rituximab also improves outcomes in patients with HIV-associated DLBCL, although this benefit in resource-rich settings is less clear in patients with CD4 cell counts of less than 50 cells per μL (ie, those with severe immunosuppression) due to the increased risk of treatment-related infectious complications. We found no prospective data for R-CHOP in patients with DLBCL in sub-Saharan Africa.

Added value of this study

To our knowledge, this is the first clinical trial of rituximab for DLBCL focused on sub-Saharan African populations, and the first clinical trial of the treatment of adults with lymphoma in this region in the current era of widespread access to HIV treatment. We enrolled patients with DLBCL who had adverse disease characteristics (ie, those that typically confer poor outcomes). No patients were lost to follow-up, and overall survival at 24 months was 55% under routine programmatic conditions, which is among the best reported outcomes to date for this population in sub-Saharan Africa.

Implications of all the available evidence

R-CHOP could be feasible, safe, and efficacious for patients with DLBCL under routine programmatic conditions in Malawi and in similar settings.
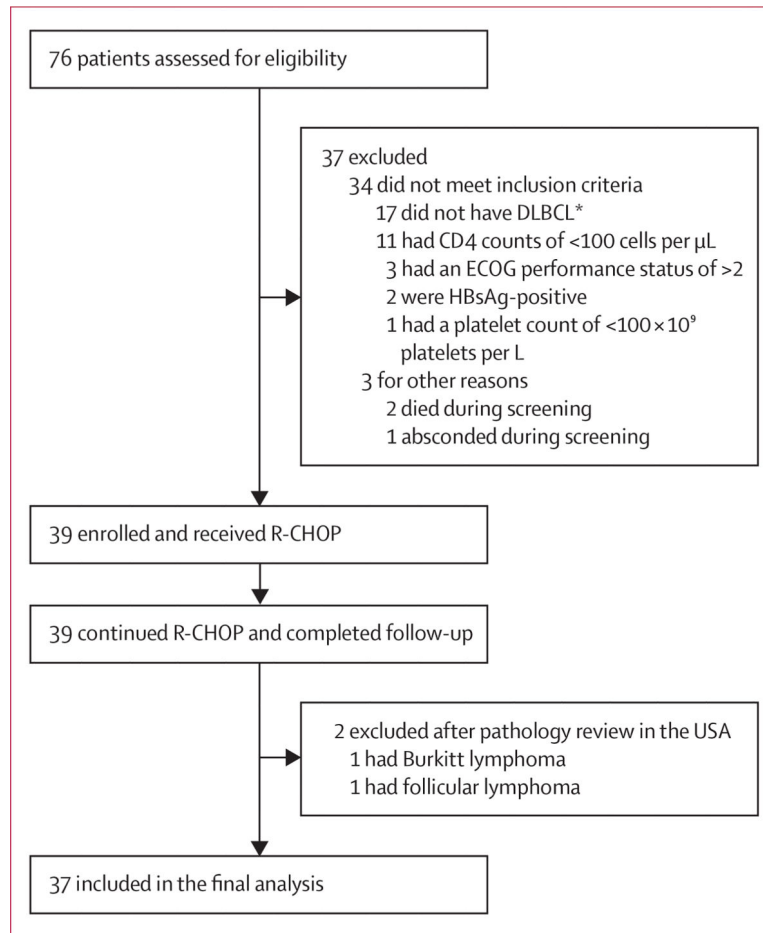
Figure 1: Trial profile

DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. *Seven patients had plasmablastic lymphoma, six had Burkitt lymphoma, three had T-cell lymphoma, and one had primary effusion lymphoma.
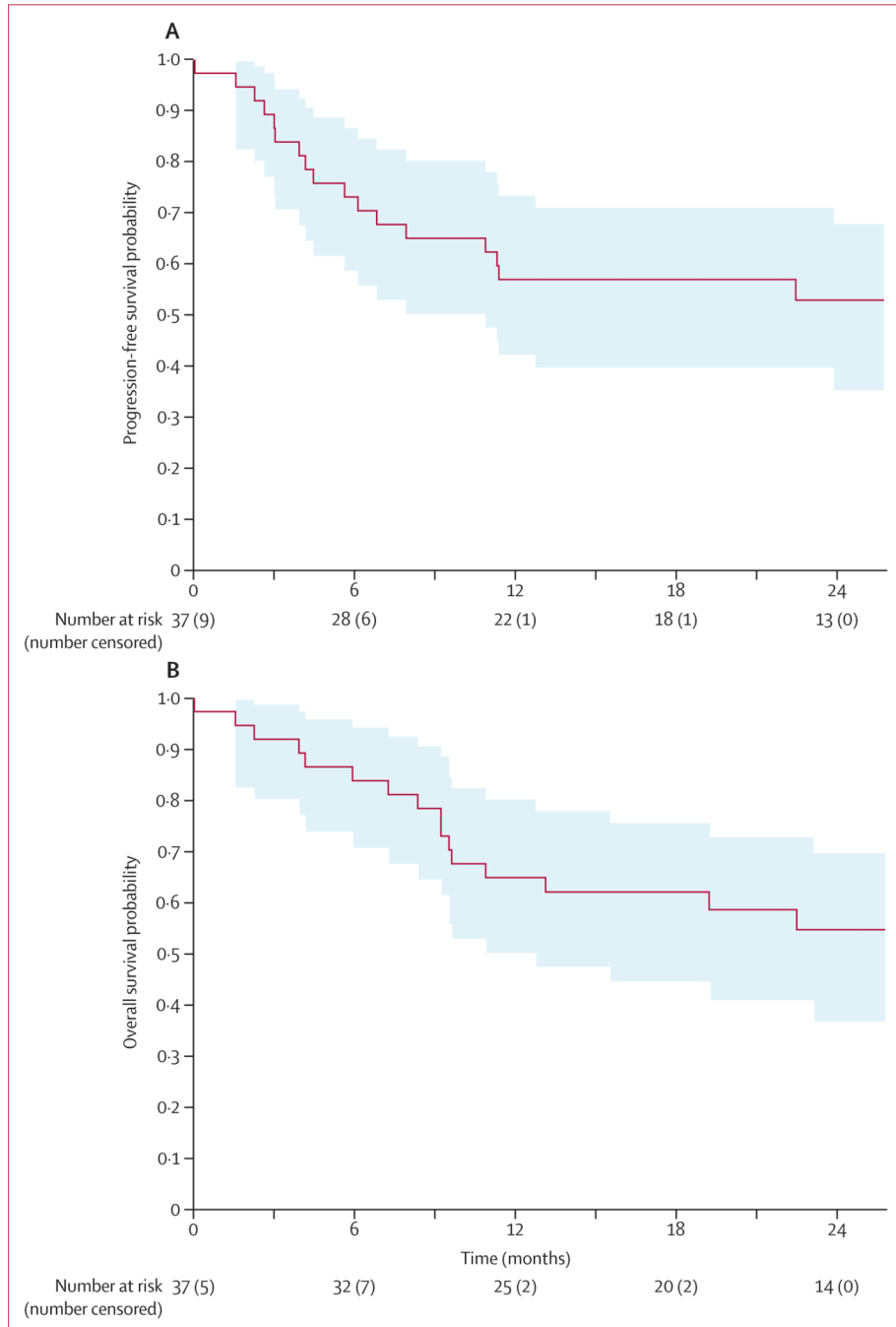
Figure 2: Progression-free (A) and overall (B) survival of patients with DLBCL in Malawi receiving R-CHOP

In A and B, the blue shaded region shows the 95% CIs. DLBCL=diffuse large B-cell lymphoma. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 1:

Baseline characteristics of patients with diffuse large B-cell lymphoma receiving R-CHOP

	All patients (n=37)	HIV-positive patients (n=27)	HIV-negative patients (n=10)	p value
Sex	..	..	..	0·61
Female	16 (43%)	11 (41%)	5 (50%)	..
Male	21 (57%)	16 (59%)	5 (50%)	..
Age, years	44 (39–49)	46 (39–50)	40 (35–49)	0·37
ECOG performance status	..	..	..	0·055
0	13 (35%)	10 (37%)	3 (30%)	..
1	13 (35%)	12 (44%)	1 (10%)	..
2	11 (30%)	5 (19%)	6 (60%)	..
Stage III or IV disease	20 (54%)	16 (59%)	4 (40%)	0·30
Palpable mass of 10 cm	15 (41%)	12 (44%)	3 (30%)	0·43
Lactate dehydrogenase, IU/L *	515 (373–692)	504 (309–692)	577 (432–740)	0·34
Age-adjusted absolute International Prognostic Index	..	..	..	0·91
0	1 (3%)	1 (4%)	0	..
1	11 (30%)	8 (30%)	3 (30%)	..
2	20 (54%)	15 (56%)	5 (50%)	..
3	5 (14%)	3 (11%)	2 (20%)	..
On ART for 3 months at diagnosis	..	21 (78%)	NA	..
Duration of ART, months	..	36 (5–86)	NA	..
CD4 count, cells per µL	..	208 (144–422)	NA	..
HIV RNA <1000 copies per mL	..	20 (74%)	NA	..
EBV-positive tumour †	2/28 (7%)	1/22 (5%)	1/6 (17%)	0·31
Tumour with GCB immunophenotype‡	16/28 (57%)	13/22 (59%)	3/6 (50%)	0·69
Ki67 expression score	80% (60–90)	83% (60–95)	75% (55–80)	0·11
Self-reported symptom duration of 6 months	25 (68%)	20 (74%)	5 (50%)	0·24
Any history of tuberculosis treatment	11 (30%)	11 (41%)	0	0·016
Tuberculosis treatment prescribed for lymphadenopathy	5/11 (45%)	5/11 (45%)	0	..

Data are n (%), median (IQR), or n/N (%). R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. ECOG=Eastern Cooperative Oncology Group. ART=antiretroviral therapy. NA=not applicable. EBV=Epstein-Barr virus. GCB=germinal centre B-cell.

*Laboratory upper limit of normal was 250 IU/L.

†Assessed by EBV-encoded RNA in-situ hybridisation.

‡Assessed by immunohistochemistry with the Hans classifier.

Table 2:

Treatment course and toxic effects in patients with diffuse large B-cell lymphoma who received R-CHOP

	All patients (n=37)	HIV-positive patients (n=27)	HIV-negative patients (n=10)	p value
Treatment course				
Number of R-CHOP cycles, median (IQR)	6 (4–6)	5 (4–6)	6 (6–6)	0·041
Completed six R-CHOP cycles	22 (59%)	13 (48%)	9 (90%)	0·021
Any treatment delay of 7 days [*]	21 (57%)	18 (67%)	3 (30%)	0·046
Any dose reduction	21 (57%)	19 (70%)	2 (20%)	0·0060
Total number of dose-reduced cycles	1(0–2)	1 (0–3)	0 (0–0)	0·013
Concentration of cyclophosphamide per cycle, mg/m^2	750 (657–750)	750 (563–750)	750 (750–750)	0·058
Concentration of doxorubicin per cycle, mg/m^2	50 (44–50)	50 (38–50)	50 (50–50)	0·061
Interval between cycles, days	21 (21–25)	22 (21–28)	21 (21–21)	0·0037
Toxic effects				
Haematological toxicity [†‡]	32 (86%)	23 (85%)	9 (90%)	0·70
Neutropenia [†]	26 (70%)	21 (78%)	5 (50%)	0·10
Anaemia [†]	11 (30%)	6 (22%)	5 (50%)	..
Thrombocytopenia [†]	0	0	0	..
Non-haematological toxicity [†]	12 (32%)	10 (37%)	2 (20%)	0·33
Infections	9 (24%)[§]	7 (26%)	2 (20%)	..
Febrile neutropenia	4 (11%)	4 (15%)	0	..
Hypersensitivity	1 (3%)	1 (4%)	0	..
Diarrhoea	1 (3%)	1 (4%)	0	..
Constipation	1 (3%)	1 (4%)	0	..
Bowel obstruction	1 (3%)	1 (4%)	0	..
Anorexia	1 (3%)	0	1 (4%)	..

Data are median (IQR) or n (%). R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

[*] Treatment was considered as delayed if the interval between cycles was 7 days or more.

[†] Grade 3 or 4 in severity.

[‡] The total number of individual grade 3 or 4 toxicities was greater than the total number of patients, as patients could have more than one event.

[§] Included Gram-negative bacteraemia (n=2), malaria (n=1), osteomyelitis (n=1), septic arthritis (n=1), cellulitis (n=2), empyema (n=1), and progressive multifocal leukoencephalopathy (n=1).