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R-CODOX-M/R-IVAC versus DA-EPOCH-R in patients with newly diagnosed Burkitt lymphoma (HOVON/SAKK): final results of a multicentre, phase 3, open-label, randomised trial

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Summary

Background Patients with newly diagnosed high-risk Burkitt lymphoma are treated with high-intensity immune-chemotherapy regimens such as R-CODOX-M/R-IVAC or with lower-intensity regimens such as DA-EPOCH-R. The aim of this study was to make a formal comparison between these regimens.

Methods This multicentre, phase 3, open-label, randomised study was done in 26 clinical centres in the Netherlands, Belgium, and Switzerland. Eligible patients were aged 18–75 years with newly diagnosed high-risk Burkitt lymphoma without CNS involvement. Patients were randomly assigned to two cycles of R-CODOX-M/R-IVAC (R-CODOX-M: rituximab 375 mg/m² on day 1 and 9, cyclophosphamide 800 mg/m² on day 1, cyclophosphamide 200 mg/m² on days 2–5, vincristine 1·5 mg/m² on days 1 and 8, doxorubicin 40 mg/m² on day 1, and methotrexate 3000 mg/m² on day 10; R-IVAC: rituximab 375 mg/m² on days 3 and 7, iphosphamide 1500 mg/m² on days 1–5, etoposide 60 mg/m² on days 1–5, and cytarabin 2000 mg/m² on day 1 and 2) or six cycles of DA-EPOCH-R (dose-adjusted etoposide 50–124 mg/m² on days 1–4, prednisolone 120 mg/m² on days 1–5, vincristine 0·4 mg/m² on days 1–4, dose-adjusted cyclophosphamide 480–1866 mg/m² on day 5, dose-adjusted doxorubicin 10–24·8 mg/m² on days 1–4, rituximab 375 mg/m² on days 1 and 5). Patients older than 65 years received a dose modified R-CODOX-M/R-IVAC. All drugs were intravenous except for prednisolone, which was oral. Patients also received four intrathecal CNS administrations with cytarabin (70 mg) and four with methotrexate (15 mg). Patients were stratified by centre, leukemic disease, and HIV-positivity. The primary endpoint was progression-fee survival. All analyses were done by modified intention-to-treat, excluding randomly assigned patients who were subsequently found to have CNS involvement or diagnosis other than Burkitt lymphoma at study entry. This study is registered with the European Clinical Trial Register, EudraCT2013-004394-27.

Findings Due to a slow accrual, the study was closed prematurely on Nov 15, 2021. Between Aug 4, 2014, and Sept 17, 2021, 89 patients were enrolled and randomly assigned to receive R-CODOX-M/R-IVAC (n=46) or DA-EPOCH-R (n=43). Five patients were excluded after random assignment (three in the R-CODOX-M/R-IVAC group [one diagnosis other than Burkitt lymphoma at study entry according to local pathology and two CNS involvement] and two in the DA-EPOCH-R group [one diagnosis other than Burkitt lymphoma at study entry according to local pathology and one CNS involvement]. 84 remaining patients were included in the modified intention-to-treat analysis. 73 (87%) of 84 patients were male, 76 (90%) presented with stage III or IV disease, and nine (11%) had HIV-positive Burkitt lymphoma. Median patient age was 52 years (IQR 37–64). With a median follow-up of 28·5 months (IQR 13·2–43·7), 2-year progression-free survival was 76% (95% CI 60–86%) in the R-CODOX-M/R-IVAC group and 70% (54–82%) in the DA-EPOCH-R group (hazard ratio 1·42, 95% CI 0·63–3·18; p=0·40). There were two deaths in the R-CODOX-M/R-IVAC group (one infection [treatment related] and one due to disease progression [not treatment related]) and one death in the DA-EPOCH-R group (COVID-19 infection [treatment related]). In the R-CODOX-M/R-IVAC group, four patients went off-protocol because of toxic effects, versus none in the DA-EPOCH-R group. Patients treated with R-CODOX-M/R-IVAC had more infectious adverse events (24 [56%] of 43 patients had at least one grade 3–5 infection *vs* 14 [34%] of 41 patients in the DA-EPOCH-R group).

Interpretation The trial stopped early, but the available data suggest that while DA-EPOCH-R did not result in superior progression-free survival compared with R-CODOX-M/R-IVAC, it was associated with fewer toxic effects and need for supportive care. DA-EPOCH-R appears to be an additional valid therapeutic option for patients with high-risk Burkitt lymphoma without CNS involvement.

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Research in context

Evidence before this study

We searched PubMed for clinical reports on Burkitt lymphoma published from database inception to July 31, 2023, using the search terms "untreated Burkitt lymphoma" AND "therapy". We identified 82 articles of which 18 reported on prospective clinical trials in first-line treatment of adults with sporadic Burkitt lymphoma. There was only one phase 3 trial. This study assessed the role of rituximab added to a backbone of high-intensity chemotherapy (LMB-89) and demonstrated survival advantage by adding rituximab. The 17 other prospective studies reported on phase 2 trials evaluating different (immune) chemotherapy regimens. 14 trials reported on high-intensity regimens, such as R-CODOX-M/R-IVAC, Hyper-CVAD, up-front autologous stem cell transplantation, German Multicentre ALL/NHL2002 protocol, and the Cancer and Leukemia Group B-9251-regimen. These different high-intensity schemes result in overall survival rates of around 75% for high-risk Burkitt lymphoma as was also confirmed in some retrospective studies.

Three trials report on lower-intensity schemes. A regimen without anthracyclines for older patients resulted in a survival rate of 57%, significantly lower than that with high-intensity schemes. The low intensity DA-EPOCH-R was first described as a mono-centre phase II trial and subsequently in a multi-centre phase II trial that reported survival rates of 100% and 87% respectively. These survival rates were deemed to be the result of two pharmaco-dynamic principles. The first is that long exposure time (and not peak concentration) is important for cell death of rapidly proliferating tumour cells such as Burkitt lymphoma cells. Secondly, variations in drug clearance form the rationale for intra-patient dose-adjustment. The advantage of this regimen is that it can be delivered on an out-hospital basis. DA-EPOCH-R does not contain high doses of CNS-penetrating drugs (such as methotrexate and cytarabine), making it unsuitable for patients with known CNS parenchymal involvement.

Added value of this study

This HOVON/SAKK 127 study compared a high-intensity regimen to a lower-intensity regimen in patients with high-risk Burkitt lymphoma without CNS involvement. Treatment with the lower-intensity DA-EPOCH-R regimen was a valid therapeutic option for high-risk Burkitt lymphoma patients without CNS involvement, and was less toxic and less expensive than the high-intensity R-CODOX-M/R-IVAC regimen.

Implications of all the available evidence

Burkitt lymphoma is a rare yet aggressive form of non-Hodgkin lymphoma, and prospective clinical trials are few. The results of this study, which is the first study comparing different chemotherapy regimens in the treatment of Burkitt lymphoma patients, will support treatment decision making. Patients treated with R-CODOX-M/R-IVAC had more infectious adverse events, received significantly more transfusions, and were admitted to hospital for significantly longer than were patients treated with DA-EPOCH-R. Both regimens resulted in 2-year overall survival rates of around 75%, which is similar to results with other high-intensity regimens. Future clinical studies should aim at improving first-line therapy for patients with Burkitt lymphoma, which might include T-cell directing therapies (for example by adding bispecific antibodies or a timely switch to chimeric antigen receptor T-cell therapy in the case of poor response).

Introduction

Burkitt lymphoma is a rare and aggressive B-cell neoplasm associated with translocation of the *MYC* oncogene to an immunoglobulin promotor.[1,2] Adults with low-risk Burkitt lymphoma without risk factors such as high lactate dehydrogenase, WHO performance status 2 or greater, stage III or IV, or mass size 10 cm or larger have a 2-year overall survival of up to 100%. By contrast, patients with high risk factors have a 2-year overall survival of 70–75%.[3–7] indicating the need of therapy improvement for these patients. The rarity of the disease has resulted in a paucity of prospective clinical trials. Thus far, only one randomised controlled trial has been done, and this trial reported the added value of rituximab to the high-intensity chemotherapy LMB-89 (lymphome malin B) backbone.[8] Rituximab is now added to all high-intensity chemotherapy backbones that have been assessed in phase 2 trials such as the German Multicentre ALL/NHL2002 regimen,[9–11] the Cancer and Leukaemia Group B (CALGB)-9251-regimen,[12] and the dose-modified R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine [oncovin], doxorubicin, methotrexate, iphosfamide, etoposide [vepesid], and cytarabine) regimen.[13–16] In 2013, Dunleavy and colleagues published data[17] on a low-intensity scheme: DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine [oncovin], cyclophosphamide, doxorubicin [hydroxydaunorubicin], and rituximab), for which hospital admission is not mandatory, by contrast to high-intensity chemotherapy regimens.[17] The reported 3-year progression-free survival for high-risk patients treated with DA-EPOCH-R was 95% (95% CI 75–99%) in this single-centre study[17] and 4-year event-free survival was 82% (73–89%) in a follow-up multicentre study.[6]

No randomised controlled trials comparing different chemotherapy backbones have been done. We designed the HOVON/SAKK 127 trial to compare the high-intensity R-CODOX-M/R-IVAC regimen to the lower-intensity DA-EPOCH-R regimen in patients with high-risk Burkitt lymphoma with the objective to confirm the earlier reported superior progression-free survival for DA-EPOCH-R in a randomised setting. Patients with CNS

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See Online for appendix

involvement were excluded, as the DA-EPOCH-R regimen does not contain high doses of CNS penetrating drugs (such as methotrexate and cytarabine). Different definitions of high-risk disease have been used in previous prospective trials.[6,17–20] For this study, we choose the definition of high-risk disease by Mead and colleagues,[19] as it was used in the first prospective trial in the R-CODOX-M/R-IVAC group of this trial.

Methods

Study design and participants

We did this investigator-initiated multicentre, international, open-label, randomised, phase 3 study in 26 centres in the Netherlands, Belgium, and Switzerland (appendix p 17, see appendix p 19 for the full protocol). The study was first designed as a randomised phase 2 study, but after updated data were released, the design was changed through a protocol amendment on June 1, 2016. More details on this design change are provided in the appendix (p 2).

Eligible patients were aged 18–75 years with newly diagnosed (sporadic and immunodeficiency-associated), high-risk Burkitt lymphoma (by local pathology diagnosis). High-risk disease was defined according to Mead and colleagues[19] (elevated lactate dehydrogenase, WHO performance status ≥2, stage III or IV, or mass ≥10 cm). HIV-positive patients were eligible (antiviral therapy was advised). Other inclusion criteria were WHO performance status 0–3 (WHO performance status 4 only if disease related), adequate haematological, renal, and hepatic laboratory tests. Patients with severe comorbidities, endemic Burkitt lymphoma, low-risk Burkitt lymphoma, or CNS involvement were excluded. CNS involvement had to be excluded by flow-cytometry of cerebrospinal fluid in all patients. Complete eligibility criteria are in the study protocol (appendix p 19).

The study was conducted in accordance with the Guidelines on Good Clinical Practice from the International Conference on Harmonization and the principles of the Declaration of Helsinki. The study protocol and all amendments were centrally approved by the Amsterdam UMC medical ethical committee and locally at each study site. All patients provided written informed consent to participate in the study. An independent data and safety monitoring committee did regular assessments of the efficacy and safety data.

Randomisation and masking

After registration, patients were randomly assigned (1:1) to either two cycles of R-CODOX-M/R-IVAC or to six cycles of DA-EPOCH-R (appendix p 3). Random assignment was done through an interactive web-based response system (Alea) at the HOVON Data Center. Patients were randomly assigned and stratified by centre, leukemic disease, and HIV-positivity, with a minimisation procedure to ensure balance within each stratum and overall balance. Each patient was given a unique patient study number (a sequence number by order of enrolment in the trial). Patient study number and result of random assignment was given immediately by the online registration database or by phone and confirmed by email. In the Alea software, the random assignment was tested by running a series of simulated trials and checking that the instructions programmed into Alea for the trial will produce a distribution of allocations in agreement with their intentions. The results of the validation process were reviewed by an independent statistician. There was no blinding or masking.

Procedures

Treatment regimens have been described previously[6,13] and are summarised in the appendix (p 9). R-CODOX-M consists of rituximab 375 mg/m² on day 1 and 9, cyclophosphamide 800 mg/m² on day 1, cyclophosphamide 200 mg/m² on days 2–5, vincristine 1·5 mg/m² on days 1 and 8, doxorubicin 40 mg/m² on day 1, and methotrexate 3000 mg/m² (in patients aged 65 years or younger) or 1000 mg/m² (patients older than 65 years) on day 10. R-IVAC consists of rituximab 375 mg/m² on days 3 and 7, iphosphamide 1500 mg/m² (in patients aged 65 years or younger) or 1000 mg/m² (in patients older than 65 years) on days 1–5, etoposide 60 mg/m² on days 1–5, and cytarabin 2000 mg/m² (in patients aged 65 years or younger) or 1000 mg/m² (in patients older than 65 years) on day 1 and 2. DA-EPOCH-R consists of dose-adjusted etoposide 50 mg/m² (50–124 mg/m² depending on dose level) on days 1–4, prednisolone 120 mg/m² on days 1–5, vincristine 0·4 mg/m² on days 1–4, dose-adjusted cyclophosphamide 750 mg/m² (480–1866 mg/m² depending on dose level) on day 5, dose-adjusted doxorubicin 10 mg/m² (10–24·8 mg/m² depending on dose level) on days 1–4, rituximab 375 mg/m² on days 1 and 5. For the exact levels of doxorubicin, etoposide, and cyclophosphamide in dose levels 1–4, see the appendix (p 9). All drugs were intravenous except for prednisolone, which was oral. Patients also received four intrathecal CNS administrations with cytarabin (70 mg) and four with methotrexate (15 mg). Timing of intrathecal administrations was at physician's choice. Patients were admitted to hospital for all therapeutic administrations of R-CODOX-M/R-IVAC. Outpatient administration of DA-EPOCH-R was allowed when feasible.

After the registration of the first 28 patients, a protocol amendment on Jan 31, 2018, allowed one cycle of R-CHOP (cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine and prednisone, plus rituximab) before random assignment. This initial R-CHOP was intended to ameliorate the clinical course of highly symptomatic Burkitt lymphoma and facilitate inclusion in the trial, as some patients cannot be without therapy until inclusion and random assignment due to disease burden and symptoms.

End of treatment response was evaluated with PET-CT scan and defined according to the Lugano criteria.[21]

Complete metabolic response was defined as Deauville score 1–3.[22] Mid-treatment response was evaluated by CT scan or PET-CT scan (investigator's choice). PET-CT evaluation and review was done by the participating centres. During follow-up, patients were evaluated every 3 months until 6 months after completion of therapy, then every 6 months until 24 months after therapy, and then annually for 5 years. During follow-up, scans were performed at the discretion of the investigator.

Central pathology review was done according to standard procedures of the HOVON Pathology Facility and Biobank (HOP) for patients enrolled in the Netherlands and Belgium (https://hovon.nl/en/working-groups/technical-committees/hop). Review for Swiss cases was done according to the same protocols. For details see the appendix (p 2).

Adverse events were reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier. Safety and toxicity was documented by the incidence of adverse events with Common Terminology Criteria for Adverse Events version 4.0. Grade 3 or worse adverse events were recorded by treatment group, cycle, and patient. Grade 1–2 events were not recorded.

Outcomes

The primary endpoint was progression-free survival by local assessment, defined as time from random assignment to the first of disease progression, relapse, or death from any cause. Patients still alive or lost to follow up were censored at the date they were last known to be alive.

Secondary endpoints were response rate at end of treatment, overall survival, event-free survival, disease-specific survival, safety, and hospital stay duration (nights). Overall survival was defined as time from date of registration until death from any cause. Follow-up of patients still alive was censored at last contact. Disease-specific survival was defined as time from date of registration until death from Burkitt lymphoma. Event-free survival was defined as time from random assignment to no complete metabolic remission at end of treatment, disease progression, relapse, or death, whichever came first.

Exploratory analyses included variables associated with outcome (prespecified), prognostic value of Burkitt Lymphoma International Prognostic Index (BL-IPI; not prespecified),[23] and cost analyses (not prespecified).

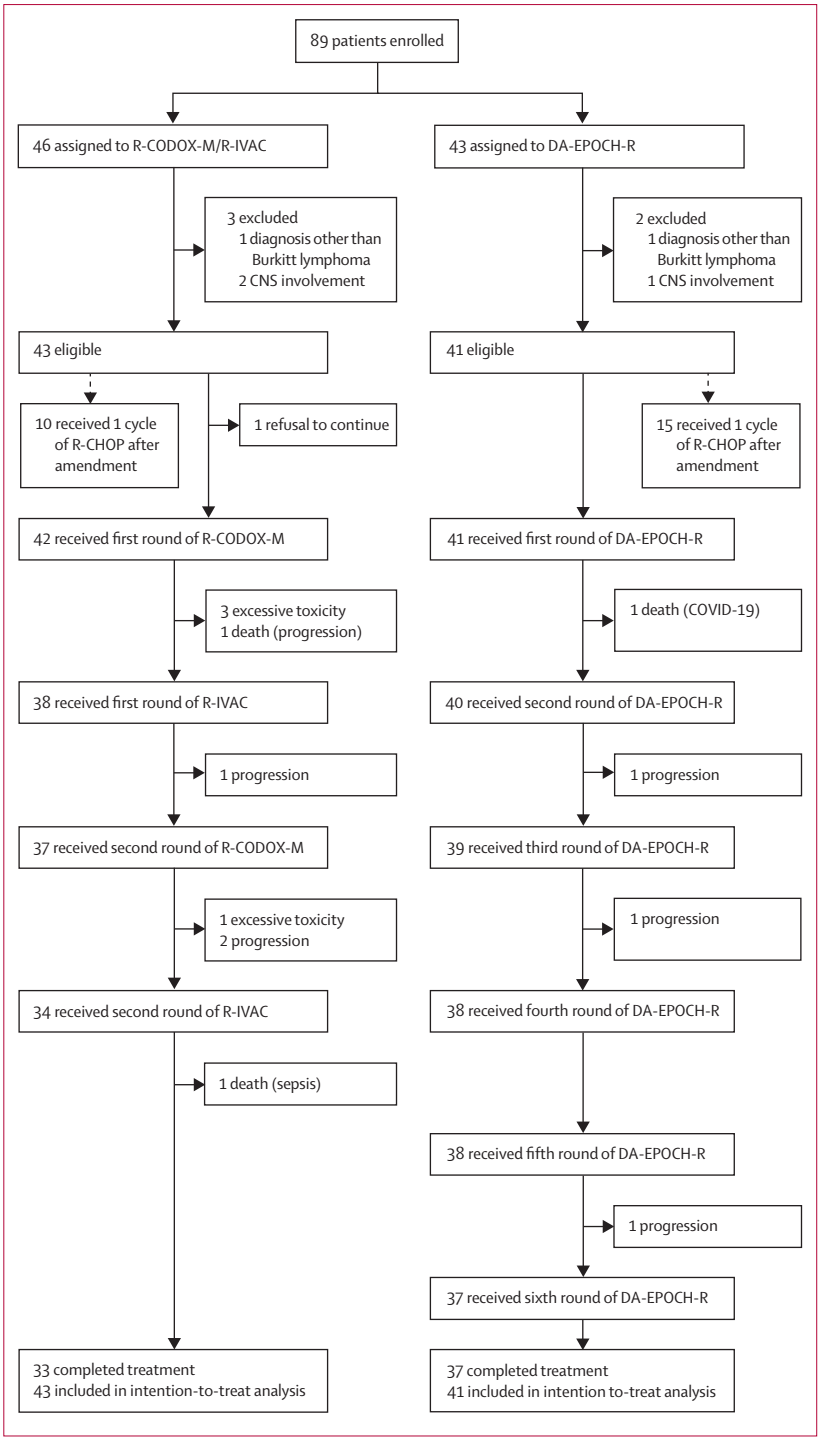

Figure 1: **Trial profile**

Statistical analysis

The primary objective of the study was to establish an increase in 2-year progression-free survival from 70% with R-CODOX-M/R-IVAC to 85% with DA-EPOCH-R. To test the hypothesis of the primary objective at a 5% significance level and with 80% power (hazard ratio [HR] 0·46), we planned a sample size of 250 patients. After 100 patients were registered, an interim analysis was planned, after which the trial would be recommended to stop for futility or modification if a lower progression-free survival in the experimental group was observed with a p value less than 0·1 (log rank test). Due to a slow

	R-CODOX-M/ R-IVAC (n=43)	DA-EPOCH-R (n=41)
Age (years)		
Median (range)	50 (18–75)	56 (20–74)
>60 years	10 (23%)	16 (39%)
Sex		
Male	37 (86%)	36 (88%)
Female	6 (14%)	5 (12%)
Ann Arbor stage		
I or II	5 (12%)	3 (7%)
III or IV	38 (88%)	38 (93%)
WHO performance status		
0–2	40 (93%)	36 (88%)
3–4	3 (7%)	5 (12%)
Mass >10 cm	20 (47%)	22 (54%)
Lactate dehydrogenase greater than upper limit of normal	31 (72%)	29 (71%)
HIV positive	5 (12%)	4 (10%)
Circulating disease		
>25% peripheral blasts	1 (2%)	2 (5%)
Bone marrow involvement		
Aspirate positive	12 (29%)	4 (11%)
Treatment before randomisation		
1 cycle of R-CHOP	10 (23%)	15 (36%)
BL-IPI		
Low	10 (23%)	8 (20%)
Intermediate	20 (47%)	19 (46%)
High	13 (30%)	14 (34%)

Data are n (%) or median (range). Ethnicity of the participants was not collected. Information on screen failures is not available. BL-IPI=Burkitt Lymphoma International Prognostic Index as defined by Olszewski and colleagues.[23]

Table 1: **Baseline characteristics**

accrual rate and the withdrawn commitment of another European Group, the study was prematurely closed for enrolment on Nov 15, 2021. Data cutoff for analysis was Dec 6, 2022.

All analyses were restricted to eligible patients. Patients randomised but considered ineligible afterwards due to exclusion criteria such as other diagnosis than Burkitt lymphoma, or CNS involvement were excluded from all analyses. This amounts to a modified intention-to-treat analysis.

We used descriptive statistics. The formal test for the difference in progression-free survival between the two treatment groups was done with a multivariate Cox regression analysis with adjustment for the two stratification factors: leukemic burden and HIV-positivity. HRs and 95% CIs were determined to estimate the treatment effect. The p value was based on the likelihood ratio test. Actuarial estimates and 95% CIs at appropriate timepoints were computed for all patients and per treatment group, and Kaplan-Meier curves were generated to illustrate survival. No corrections for multiple testing were required and all analyses on the secondary endpoints had exploratory purposes only. The predictive value of patient-related factors for response and survival endpoints was evaluated univariately and multivariately by use of Cox regression.

Data were analysed using Stata version 15. Monitoring was done by HOVON and SAKK. A data safety monitoring board was established to review the general progress and feasibility of the trial, the quality and completeness of the data, adverse events, and safety. This study is registered with the European Clinical Trial Register, EudraCT2013-004394-27.

Role of the funding source

The study was supported by grants of The Dutch Cancer Society and the Schumacher-Kramer Foundation. Funders had no role in collection, analysis, interpretation of the data, or writing of the manuscript.

Results

Between Aug 4, 2014, and Sept 17, 2021, 89 patients were enrolled and assigned to R-CODOX-M/R-IVAC (n=46) or DA-EPOCH-R (n=43; figure 1). Five patients were excluded after random assignment (three in the R-CODOX-M/R-IVAC group [one diagnosis other than Burkitt lymphoma at study entry according to local pathology and two CNS involvement] and two in the DA-EPOCH-R group [one diagnosis other than Burkitt lymphoma at study entry according to local pathology and one CNS involvement]). 84 remaining patients were included into the modified intention-to-treat analysis. Baseline characteristics are presented in table 1. 73 (87%) of 84 patients were male. Median patient age was 52 years (IQR 37–64). 76 (90%) of 84 patients presented with stage III or IV disease. Nine (11%) of 84 patients had HIV-positive Burkitt lymphoma. According to the proposed BL-IPI classification,[23] 18 (21%) of 84 patients presented with low-risk disease, 39 (46%) presented with intermediate-risk disease, and 27 (32%) presented with high-risk disease. After a protocol amendment on Jan 31, 2018, ten patients in the R-CODOX-M/R-IVAC group and 15 patients in the DA-EPOCH-R group received one cycle of R-CHOP before random assignment (12 patients completed six cycles of DA-EPOCH-R after an initial cycle of R-CHOP). In the R-CODOX-M/R-IVAC group, one patient refused treatment before start of protocol treatment and nine patients discontinued treatment due to progression (n=4), excessive toxicity (n=4), and sepsis (n=1). There were two deaths during the treatment phase (one progression and one sepsis). The patients that went off protocol due to excessive toxic effects were 47, 59, 68, and 72 years old. In the DA-EPOCH-R group, four patients discontinued treatment due to progression (n=3), or COVID-19 (n=1; during treatment phase). 33 patients in the R-CODOX-M/R-IVAC group and 37 patients in the DA-EPOCH-R group completed treatment.

Median follow-up was 28·5 months (IQR 13·2–43·7). All patients who completed treatment (figure 1) had at least

12 months of follow-up. The 1-year progression-free survival rate was 76% (95% CI 60–86%) in the R-CODOX-M/R-IVAC group and 73% (57–84%) in the DA-EPOCH-R group (figure 2A). The 2-year progression-free survival rate was 76% (60–86%) In the R-CODOX-M/R-IVAC group and 70% (54–82%) in the DA-EPOCH-R group. The estimated HR for the primary outcome (unadjusted) was 1·47 (95% CI 0·66–3·28; p=0·34). The estimated HR for progression-free survival with adjustment for leukemic burden and HIV-positivity was 1·42 (95% CI 0·63–3·18, p=0·40; full Cox model in the appendix [p 11]). There were ten events in the R-CODOX-M/R-IVAC group (eight Burkitt lymphoma progression or relapse and two deaths) and 15 events in the DA-EPOCH-R group (12 Burkitt lymphoma progression or relapse and three deaths). Three events appearing after 24 months were not Burkitt lymphoma progression related (one complication of allogeneic stem cell transplantation, two secondary malignancies). No CNS relapses were found in either group.

The 1-year overall survival rate was 78% (95% CI 62–88%) in the R-CODOX-M/R-IVAC group and 80% (65–86%) in the DA-EPOCH-R group (figure 2B). The 2-year overall survival rate was 76% (60–86%) in the R-CODOX-M/R-IVAC group and 75% (59–86%) in the DA-EPOCH-R group (HR 1·21, 95% CI 0·53–2·76; p=0·65). Ten patients died in the R-CODOX-M/R-IVAC group (seven Burkitt lymphoma, two infections, and one complication of treatment). 13 patients died in the DA-EPOCH-R group (eight Burkitt lymphoma, two infections, two secondary malignancies [oesophageal and urothelial carcinoma], and one complication of allogeneic stem cell transplantation). The two deaths in the DA-EPOCH-R group after 24 months were not related to Burkitt lymphoma progression (one secondary malignancy and one complication of allogeneic stem cell transplantation), resulting in 1-year disease-specific survival of 84% (95% CI 67–93%) with R-CODOX-M/R-IVAC and 83% (67–91%) with DA-EPOCH-R, and 2-year disease-specific survival of 82% (65–91%) with R-CODOX-M/R-IVAC and 80% (64–90%) with DA-EPOCH-R (HR 1·10, 0·40–3·02; p=0·86, figure 2C). Event-free survival curves are shown in the appendix (p 5). 1-year event-free survival was 62% (95% CI 45%–75%) in the R-CODOX-M/R-IVAC group and 66% (95% CI 49%–78%) in the DA-EPOCH-R group (HR 0·84, 0·41–1·79; p=0·64). 2-year event-free survival rates were 62% (45%–75%) and 63% (47%–76%), respectively (appendix p 5).

The numbers of HIV-positive patients (five in the R-CODOX-M/R-IVAC group and four in the DA-EPOCH-R group) and patients with circulating disease (two in the R-CODOX-M/R-IVAC group and one in the DA-EPOCH-R group) were too small to warrant a comparison in the outcomes of HIV-positive or negative and with or without circulating disease patients.

In the R-CODOX-M/R-IVAC group, dose adjustments for the different components were made in a mean of 9% of cycles (SD 2·9). Most adjustments were made for

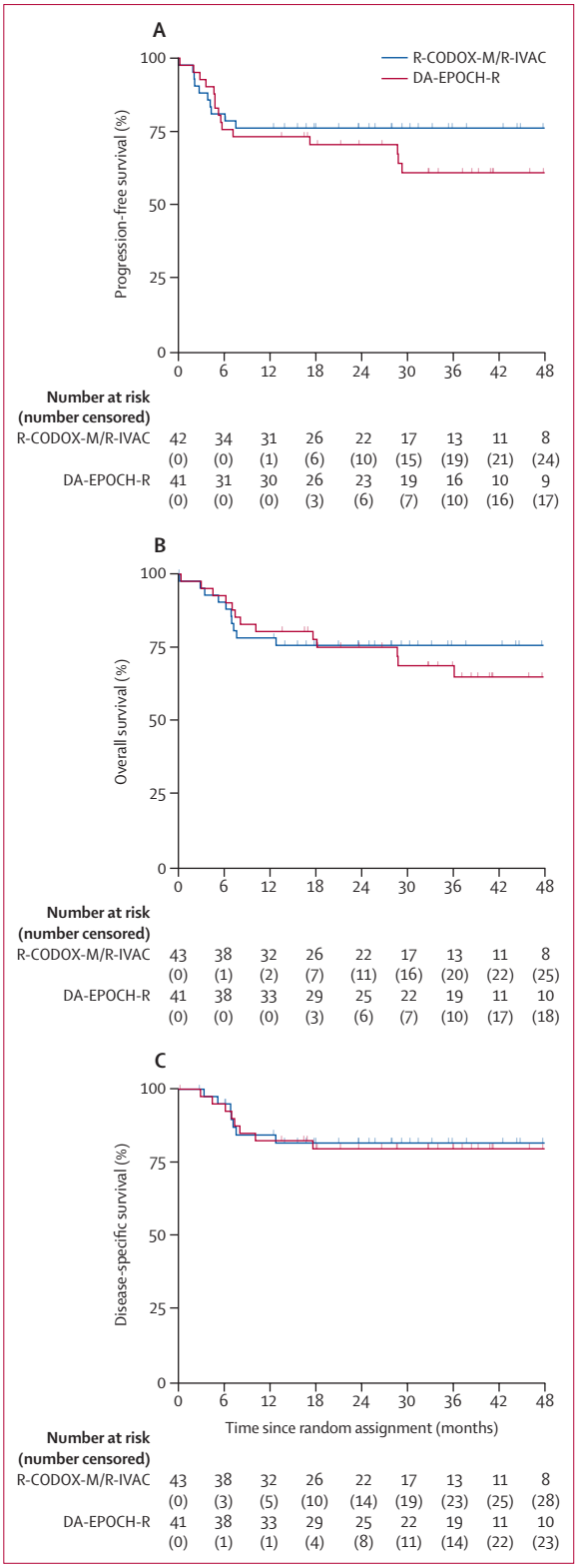

Figure 2: **Kaplan-Meier survival curves**
(A) Progression-free survival. (B) Overall survival. (C) Disease-specific survival.

	R-CODOX-M/R-IVAC				DA-EPOCH-R			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Total unique patients	31	13	2	34	29	9	1	30
Infectious								
Total	20	4	1	24	13	2	1	14
Febrile neutropenia	12	0	0	12	8	0	0	8
Sepsis	0	3	1	4	1	1	0	2
Fever unknown origin	2	0	0	2	0	0	0	0
Pulmonary infection	2	0	0	2	2	1	1	3
Infectious other	11	1	0	12	6	0	0	6
Gastrointestinal								
Total	15	3	0	16	11	0	0	11
Mucositis and diarrhoea	11	2	0	12	9	0	0	9
Elevated hepatic values	5	1	0	5	2	0	0	2
Haematological								
Total	10	6	0	12	2	4	0	5
Neutropenia	2	4	0	6	1	3	0	3
Anaemia	6	0	0	6	1	0	0	1
Trombocytopenia	5	2	0	6	0	2	0	2
Pancytopenia	1	0	0	1	0	0	0	0
Metabolic								
Total	4	1	0	4	5	2	0	6
Metabolic	4	1	0	4	5	1	0	5
Tumour lysis syndrome	0	0	0	0	1	1	0	1
Other								
Total	10	3	1	11	13	1	0	14
Neurologic	3	0	0	3	5	1	0	6
Respiratory (non infectious)	2	1	0	2	2	0	0	2
Cardiac	1	1	1	3	1	0	0	1
Musculoskeletal	1	0	0	1	2	0	0	2
Vascular	6	0	0	6	2	0	0	2
Other	1	2	0	3	4	0	0	4

Data are n. Total number of adverse events and number of unique patients who had at least one grade 3 or worse adverse event. Grade 1 and 2 adverse events were not reported as per protocol.

Table 2: **Adverse events**

vincristine in a mean of 12·5% of cycles (2·1) and for methotrexate in a mean of 11% of cycles (4·2; appendix p 4). In the DA-EPOCH-R group, Dose level 1 was the maximum in 35%, dose level 2 was the maximum in 19%, dose level 3 was the maximum in 24% and dose level 4 was the maximum in 22% of patients (appendix p 4). There was no difference in outcome between patients treated with DA-EPOCH-R that reached maximum DL4 versus DL1, although groups were too small to draw meaningful conclusions (data not shown).

Response evaluation at end of treatment was done with PET-CT scan in 34 (79%) of 43 patients in the R-CODOX-M/R-IVAC group and in 37 (90%) of 41 patients in the DA-EPOCH-R group, and revealed complete metabolic response in 28 (65%) and 27 (66%) patients respectively (p=0·94). Details on end of treatment and mid-treatment evaluation, including negative and positive predictive values for interim and end of treatment evaluation, can be found in the appendix (p 10).

Adverse events are summarised in table 2 and in the appendix (pp 6, 12). In the R-CODOX-M/R-IVAC group, 129 adverse events grade 3–5 were observed in 34 unique patients, compared with 83 adverse events in 30 patients in the DA-EPOCH-R group. Patients in the R-CODOX-M/R-IVAC group seem to have more infectious adverse events than those in the DA-EPOCH-R group (24 [56%] of 43 patients had at least one grade 3–5 infectious adverse event compared with 14 [34%] of 41 patients in the DA-EPOCH-R group; p=0·05). 12 (28%) patients in the R-CODOX-M/R-IVAC group had at least one grade 3–5 haematological adverse event compared with five (12%) patients in the DA-EPOCH-R group. 16 (37%) patients in the R-CODOX-M/R-IVAC group had at least one grade 3–5 gastrointestinal adverse event compared with 11 (27%) in the DA-EPOCH-R group.

In patients older than 60 years, nine (90%) of 10 patients treated with R-CODOX-M/R-IVAC had at least one grade 3–5 adverse event, compared with 12 (75%) of 16 patients treated with DA-EPOCH-R. Most of the serious adverse events were infectious (including febrile neutropenia) and most were found in the R-CODOX-M/R-IVAC group (n=22 *vs* 13 in the DA-EPOCH-R group; appendix p 12).

In the R-CODOX-M/R-IVAC group, patients received a median of five (IQR 2–8) red blood cell transfusions versus one (0–4) in the DA-EPOCH-R group (p<0·0001; table 3). Patients in the R-CODOX-M/R-IVAC group received a median of two (IQR 0–4) platelet transfusions versus 0 (0–0) in the DA-EPOCH-R group (p<0·0001).

Patients in the DA-EPOCH-R group received growth-factors as per protocol a median 51 days [IQR 49–60] versus 27 days (20–34) in the R-CODOX-M/R-IVAC group (p<0·0001).

In the R-CODOX-M/R-IVAC group, patients were admitted to hospital for a median 43 nights (IQR 30–60) versus 28 nights (13–33) in the DA-EPOCH-R group (p<0·0001). Hospital admissions for adverse events were similar between the groups (median 2 nights in the R-CODOX-M/R-IVAC group *vs* 0 nights in the DA-EPOCH-R group).

Analyses of different variables (age more than or less than 40 years, age more or less than 60 years, WHO performance status, lactate dehydrogenase less than limit of normal [ULN], 1–3 ULN, or more than 3 times ULN, tumour mass more than 10 cm and BL-IPI) were done (BL-IPI post-hoc) to identify factors associated with treatment outcome and survival (appendix pp 7–8). Combining both treatment groups, only WHO performance status 0 was significantly associated with better overall survival and progression-free survival (p=0·02 and p=0·01 by Kruskal Wallis; appendix p 7). No

statistically significant variables could be identified when analysed in the two treatment groups separately.

Overall survival of patients older than 60 years was not different between treatment groups (appendix p 8). In this study, all patients presented with high-risk disease according to Mead[13,19] as to the inclusion criteria per protocol. High-risk disease as defined by BL-IPI score[23] had no prognostic value in either treatment group, presumably due to small numbers (appendix p 8). In patients with high-risk BL-IPI, there was no significant difference in outcome between the two treatment regimens (appendix p 8).

From 87 (98%) of 89 patients, including all 84 treated patients, biopsy material was received for central pathology review. A diagnosis of Burkitt lymphoma was confirmed in 74 (88%) of 84 patients by immunohistochemistry or *MYC*, *BCL2*, and *BCL6*-flourescence in situ hybridisation (FISH) analysis. In 67 of these 74 patients, Burkitt lymphoma diagnosis was confirmed by both classical FISH and immunohistochemistry analysis (appendix p 2). FISH data were absent in three patient samples and four patient samples did not show a complete classic immunohistochemistry phenotype of Burkitt lymphoma (no *BCL6* expression). However, in these seven patients, the diagnosis could be substantiated by immunohistochemistry for CD38 (positive) and CD44 (negative).

In one of 84 patients, a diagnosis of high-grade B-cell lymphoma with *MYC*, *BCL2*, and *BCL6* rearrangement was rendered, five patients were classified as high-grade B-cell lymphoma, not otherwise specified, and two samples were classified as diffuse large B-cell lymphoma. In two patients, a definite diagnosis could not be rendered (unclassifiable) due to insufficient material. All clinical correlations were made based on the original including diagnosis of Burkitt lymphoma by the local pathologist.

We calculated the total costs of both regimens based on the actual days of hospital admission, administered supportive care, and drug costs according to Dutch prices (appendix pp 2, 13). The costs of a full regimen with R-CODOX-M/R-IVAC were €78 000 versus €48 000 for DA-EPOCH-R. This difference in cost was mainly due to hospital costs (€44 000 *vs* €23 000) and transfusion costs (€5000 *vs* €500) for R-CODOX-M/R-IVAC and DA-EPOCH-R, respectively.

	R-CODOX-M/R-IVAC	DA-EPOCH-R	p value
Platelet transfusions (n)			
Median (IQR)	2 (0–4)	0	..
Mean (SD)	4 (7)	0 (1)	..
Range	0–37	0–6	..
p value	..	..	<0·0001
Red blood cell transfusions (n)			
Median (IQR)	5 (2–8)	1 (0–4)	..
Mean (SD)	7 (7)	3 (4)	..
Range	0–28	0–17	..
p value	..	..	<0·0001
Days of filgrastim per protocol			
Median (IQR)	28 (20–34)	57 (49–60)	..
Mean (SD)	27 (13)	51 (17)	..
Range	0–56	1–81	..
p value	..	..	<0·0001
Hospital admission planned per protocol (nights)			
Median (IQR)	43 (30–60)	28 (13–33)	..
Mean (SD)	46 (24)	25 (14)	..
Range	0–99	4–78	..
p value	..	..	<0·0001
Hospital stay for adverse events (nights)			
Median (IQR)	2 (0–10)	0 (0–3)	..
Mean (SD)	9 (18)	3 (7)	..
range	0–99	0–37	..
p value	..	..	0·11

Numbers of red blood cell and platelet transfusions, days of growth factor support, and hospital admission nights (planned and for adverse events) by treatment group.

Table 3: **Supportive care**

Discussion

To our knowledge, this is the first multi-centre, randomised study to compare two different immune-chemotherapy regimens (high-intensity R-CODOX-M/R-IVAC *vs* low-intensity DA-EPOCH-R) in patients with high-risk Burkitt lymphoma, showing that treatment with DA-EPOCH-R did not result in superior complete metabolic response and survival outcomes compared with R-CODOX-M/R-IVAC, but was associated with less toxic effects and less need for supportive care.

Patients with CNS involvement were excluded, as the DA-EPOCH-R regimen does not contain high doses of CNS penetrating drugs (such as methotrexate and cytarabine).

Enrolment in the study was slower than expected. The main reasons were the COVID-19 pandemic and several centres failing to activate the study.

Treatment with DA-EPOCH-R resulted in similar response and survival outcomes as R-CODOX-M/R-IVAC, however this result is inconclusive as the trial has less power due to the premature closure of the study. We did a futility analysis with the available survival data and calculated the probability of showing superiority with DA-EPOCH-R, which revealed a conditional power of only 20%. If an interim analysis had been done, as was initially projected after 100 patients, the conclusion that it would be futile to continue the study would have been drawn (based on a lower progression-free survival in the experimental group, with a $p<0·1$).

Although we could not prove superiority with DA-EPOCH-R, this study has provided valuable information. First, administration of both regimens was feasible. R-CODOX-M/R-IVAC cycles were fully dosed in

91% of cycles and DA-EPOCH-R dose increasements were similar to earlier published data,[6] reflecting adherence to planned treatment. Second, more toxic effects were seen in the R-CODOX-M/R-IVAC group than in the DA-EPOCH-R group.

Third, patients treated with R-CODOX-M/R-IVAC needed significantly more supportive care and were admitted to hospital for significantly more time than were patients treated with DA-EPOCH-R.

Exploratory subgroup analyses revealed that only WHO performance status 0 was significantly associated with better overall survival. High-risk disease as defined by BL-IPI score (two or more of age ≥40 years, performance status ≥2, lactate dehydrogenase >3 ULN, and CNS involvement)[23,24] had no prognostic value, presumably due to small numbers.

Finally, we were able to calculate the actual real costs for both groups. The price of a full regimen with R-CODOX-M/R-IVAC was €78 000 versus €48 000 for DA-EPOCH-R, which could be lowered to €37 000 when all administrations were done on an outpatient basis. The study population in this study reflects clinical practice, allowing HIV-positive and patients with circulating disease to be enrolled. All patients received intrathecal CNS prophylaxis and no CNS relapses have occured.

Apart from the premature closure and small numbers for subgroup analyses, this study has limitations. Although median follow-up was more than 24 months and total follow-up was more than 12 months for all patients that completed treatment, this was still too short to assess long-term toxicity. Long-term toxicity might vary as a result of the different components of the regimens (eg, R-CODOX-M/R-IVAC contains more than twice the dose of alkylating drugs [cyclophosphamide and iphosfamide] as DA-EPOCH-R). However, the infusion duration of anthracyclines of 6 h or longer, such as in DA-EPOCH-R, is associated with a lower cardiotoxicity profile than is shorter infusion duration.[25]

As no effective salvage options exist, future clinical studies should aim at improving first-line therapy, which might include T-cell directing therapies (adding bispecific antibodies or a timely switch to chimeric antigen receptor T-cell therapy in case of poor response).

The results of this study can support treatment decision making. The two regimens are options to discuss with patients diagnosed with Burkitt lymphoma without CNS involvement. Noteworthy differences are duration of treatment (full regimen of ≥16 weeks for R-CODOX-M/R-IVAC versus ≥18 weeks for DA-EPOCH-R), higher toxicity and transfusion rates with R-CODOX-M/R-IVAC, and the possibility of outpatient treatment with DA-EPOCH-R.

In conclusion, the available data suggest that treatment with DA-EPOCH-R is not superior compared with R-CODOX-M/R-IVAC, but it is associated with less toxic effects and significantly less supportive care. Treatment with DA-EPOCH-R is a valid, less toxic and less expensive therapeutic option for high-risk Burkitt lymphoma in patients without CNS involvement.

Contributors

MC, FS, MN, PL, and GvI designed the protocol and were involved in data collection, data interpretation and patient accrual, enrolment, and treatment. DC provided statistical design and analyses. UN, MM, PG, WS, TZ, KW, AD, MK, WT, LT, DD, EvdN, MG, HV, LB, CC, and PM were involved in patient accrual, enrolment, and treatment. JR performed central study coordination, RS performed central data management. LP facilitated central pathology review. RS and CU performed costs analyses. SD, MvdB, and DdJ performed pathology review. All authors had full access to all the data in the manuscript and had final responsibility for the decision to submit for publication. MC and DC directly accessed and verified the underlying data and statistical analyses were reviewed by an independent statistician.

Declaration of interests

MC declares research support from BMS, Gilead, and GenMab and participation in advisory Board for AbbVie, Novartis, and Incyte. FS declares consulting fees from Roche, Merck, and Pfizer and travel support from Roche and BMS. UN declares consulting fees from Janssen-Cilag, Celgene (BMS), Takeda, AstraZeneca, Roche, Novartis, Incyte, Beigene, Kyowa Kirin, Gilead, and Pierre Fabre, payment for lectures from Celgene (BMS), Novartis, Takeda and Gilead and travel support from Janssen, Roche, Gilead, and Takeda. MM declares consulting fees from Janssen-Cilag, CDR Life, and GSK, and payment for lectures from Janssen Cilag and BMS, participation in Data Safety Monitoring Board or Advisory Board from BMS. TZ declares consulting fees from AZD, Beigene, AbbVie, Janssen, Novartis, Lilly, Roche, BMS, and Gilead, and payment for lectures from AZD, Beigene, AbbVie, Janssen, Novartis, Lilly, Roche, BMS, and Gilead. MK declares research funding from Celgene, Kite, Takeda and Roche, and consulting fees from BMS/Celgene, Kite, Miltenyi, Novartis, and Roche, and travel support from Kite, Miltenyi, Novartis, and Roche. DD declares research funding from Alexion, and consulting fees from Alexion, Astellas, BMS, Gilead, Incyte, Janssen, Novartis, Roche, Sanofi, Servier, Sobi, and Takeda and travel support from Sobi. CU reports research support from Boehringer Ingelheim, Astellas, Celgene, Sanofi, Janssen-Cilag, Bayer, Amgen, Genzyme, Merck, Gilead, Novartis, AstraZeneca, Roche, NIH, and Ascertain. MN declares research support from Takeda, travel support from AbbVie and participation in Data Safety Monitoring Board or Advisory Board from AbbVie. PL declares research support from Takeda, consulting fees from Y-mAbs Therapeutics, payment for lectures from Lilly, AbbVie and GenMAb, travel support from Celgene and participation in Data Safety Monitoring Board or Advisory Board from AbbVie, GenMAb, Roche, Regeneron and Incyte. All the other authors declare no competing interests.

Data sharing

The data presented in this study are available on request, see the HOVON website (www.hovon.nl) for HOVON Policy Data Sharing. The data are not publicly available due to specific conditions extended by the HOVON foundation, as owner of data collected in HOVON studies.

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