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Excellent real-world outcomes of adults with Burkitt lymphoma treated with CODOX-M/IVAC plus or minus rituximab

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Summary

Treatment of Burkitt lymphoma (BL) with intensive, multi-agent chemotherapy with aggressive central nervous system (CNS) prophylaxis results in high cure rates, although no regimen is standard of care. We examined population-based survival outcomes of adults with BL treated with a modified combination of cyclophosphamide, vincristine, doxorubicin, prednisone and systemic high-dose methotrexate (MTX) (CODOX-M) with IVAC (ifosfamide, mesna, etoposide, cytarabine and intrathecal MTX) (CODOX-M/IVAC) ± rituximab over a 15-year period in British Columbia. For the 81 patients identified (including 8 with CNS involvement and 18 with human immunodeficiency virus-associated BL), 5-year progression-free survival (PFS) and overall survival (OS) were 75% [95% confidence interval (CI): 63–83%] and 77% (95% CI: 66–85%), respectively, with no treatment-related deaths. Those who completed the regimen per protocol (n = 38) had significantly improved 5-year PFS 86% (P = 0·04) and OS 92% (P = 0·008), as did those under 60 years with 5-year PFS 82% (P = 0·005) and OS 86% (P = 0·002), which remained significant in multivariate analysis [PFS: hazard ratio (HR) 3·36, P = 0·018; OS HR 4·03, P = 0·012]. Incorporation of high-dose systemic methotrexate also significantly affected multivariate survival outcomes (OS HR 0·28, P = 0·025). Stem cell transplant in first remission had no effect on OS or PFS. This large, real-world analysis of BL patients treated with CODOX-M/IVAC ± rituximab demonstrates excellent survival outcomes comparable to clinical trials. These results help to serve as a benchmark when comparing curative therapies for BL patients as novel regimens are incorporated into clinical practice.

Keywords: Burkitt lymphoma, chemotherapy, stem cell transplant, population-based, treatment.

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma (NHL) characterized by cytogenetic translocations involving the *MYC* oncogene on chromosome 8 (Erikson *et al*, 1982). The prevalence of sporadic BL accounts for <1% of adult NHL in the United States (Morton *et al*, 2006). Due to the low incidence of BL, there has not yet been a randomized trial to identify the optimum initial therapy and no standard currently exists. Multiple intensive regimens have demonstrated effectiveness in BL, including short-duration combination chemotherapy regimens (Magrath *et al*, 1996; Divine *et al*, 2005; Hoelzer *et al*, 2014; Ribrag *et al*, 2016), acute lymphoblastic leukaemia-like regimens with stepwise induction, consolidation and maintenance therapy (e.g. HyperCVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, with methotrexate and cytarabine) (Thomas *et al*, 1999), and infusional chemotherapy protocols with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (EPOCH-R) (Dunleavy *et al*, 2013; Roschewski *et al*, 2017). All of these regimens involve aggressive multi-agent chemotherapy combinations with central nervous system (CNS) prophylaxis. High-dose chemotherapy and stem cell transplant (SCT) has also been used for treatment of BL in first remission with long term progression-free survival (PFS) reported of 51–72% (Sweetenham *et al*, 1996; van Imhoff *et al*, 2005; Song *et al*, 2006);

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however, SCT in first remission has largely been replaced by more intensive up-front treatment regimens.

In 1996, the use of an intensive multiagent chemotherapy regimen among 41 BL patients which demonstrated a 2-year event-free survival (EFS) of 92% was described (Magrath *et al*, 1996). The initial protocol consisted of alternating cycles of CODOX-M (combination of cyclophosphamide, vincristine, doxorubicin, prednisone, and systemic high-dose methotrexate [MTX]) with IVAC (ifosfamide, mesna, etoposide, cytarabine, and IT MTX) (Magrath *et al*, 1996). Since the initial report, additional phase II clinical trials have demonstrated the efficacy of the Magrath regimen in adults with BL or Burkitt-like lymphoma with dose-modifications (adjustments made to vincristine, intrathecal (IT) cytarabine, cyclophosphamide and systemic MTX to decrease toxicity). Together, these trials demonstrated 2-year PFS 64%, EFS 65%, and overall survival (OS) ranging between 67% and 73% (Mead *et al*, 2002, 2008; Lacasce *et al*, 2004). Rituximab incorporation into intensive chemotherapies has also become standard practice. A phase II trial conducted by Evens *et al* (2013) showed rituximab to be well tolerated when added to the CODOX-M/IVAC regimen. Subsequently, a recent large randomized trial demonstrated that incorporation of rituximab into the short intensive Lymphome Malin B (LMB) chemotherapy regimen significantly increased 3-year EFS from 62% to 75% and 3-year OS from 70% to 83% among human immunodeficiency virus (HIV) negative BL patients, with no difference in adverse events (Ribrag *et al*, 2016).

In the province of British Columbia (BC), with a population of 4·5 million, BL patients receive uniform therapy based on era-specific BC Cancer guidelines (www.bccancer.bc.ca). A publicly funded system ensures healthcare access for all BL patients in BC under the supervision of a network of oncologists and haematologists, and all BCCA-Cancer approved therapies are funded through a central payer. The CODOX-M/IVAC regimen has been the standard treatment for BL in BC since 2001, with rituximab added as of 2004, and remains the preferred first line treatment option. New therapeutic regimens (such as dose-adjusted EPOCH-R) are currently under investigation in clinical trials (Dunleavy *et al*, 2013); however, it remains challenging to compare these regimens without the availability of a "gold standard". This study aims to evaluate the population-based survival outcomes of BL patients in BC treated with a modified Magrath regimen to help guide future treatment decisions and compare upcoming novel regimens.

Methods

Study design

The Leukemia/Bone Marrow Transplant Program of BC database, Providence Hematology database and BC Cancer Lymphoid Cancer and Lymphoma Pathology databases were queried and cross-referenced to identify all adult cases of BL diagnosed and treated with the Magrath regimen between 1 January 2001 and 31 December 2015. These three centres are the only centres in the province which treat BL. A diagnosis of BL was confirmed by expert haematopathology central review based on a diagnostic bone marrow and/or lymph node biopsy demonstrating the typical morphological, immunophenotypic, and genetic findings of BL, including the presence of a *MYC* rearrangement detected by fluorescence *in situ* hybridization, as per the World Health Organization 2001 and 2008 classifications.(Jaffe *et al*, 2001; Swerdlow *et al*, 2008) Patients diagnosed with B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma (DLBCL) and BL were excluded.

Initial evaluation of BL patients at our centres included complete blood counts and chemistries; determination of HIV status; computed tomography (CT) scans of the neck, chest, abdomen, and pelvis; bone marrow aspirate and biopsy; and a lumbar puncture with cerebrospinal fluid analysis for cytology and flow cytometry. Patients were considered low-risk if they had Ann Arbor stage 1 or 2 disease, low bulk $\leq$5 cm, normal lactate dehydrogenase (LDH), and no marrow, blood or CNS involvement; all other patients were considered high-risk. Imaging was reviewed to identify extranodal involvement and staging information. Response was assessed per the Cheson criteria (Cheson *et al*, 1999, 2007). Most patients underwent an interim imaging assessment, typically between cycles 1B and 2A, and all patients underwent final, end of treatment imaging assessments. Where an imaging assessment was not performed, clinical remission status, as assessed by the treating haematologist, was documented. This study was approved by the University of BC and BC Cancer Research Ethics Boards.

Treatment

Patients were treated with a dose-modified Magrath regimen based upon Lacasce et al (Lacasce *et al*, 2004) briefly described below and shown in Fig 1. Regimen A (CODOX-M$\pm$R) consisted of cyclophosphamide 800 mg/m^2 on days 1 and 2, doxorubin 50 mg/m^2 IV on day 1, vincristine 1·4 mg/m^2 on days 1 and 8 (capped at 2 mg total), IV MTX 3000 mg/m^2 on day 10 and IT cytarabine 50 mg on days 1 and 3. Leucovorin rescue was started on day 11 until the MTX level was <0·1 μmol/l and granulocyte colony-stimulating factor (G-CSF) was given from days 13 to 18. Regimen B (IVAC$\pm$R) was initiated upon count recovery [absolute neutrophil count (ANC) >1 × 10^9/l and platelet count >100 × 10^9/l] and consisted of ifosfamide 1500 mg/m^2, mesna 375 mg/m^2 and etoposide 60 mg/m^2 from days 1 to 5, cytarabine 2000 mg/m^2 IV on days 1 and 2, and IT MTX 12 mg on days 6 and 18. G-CSF was administered from days 7 to day 18. Rituximab was added as of 2004 at a dose of 375 mg/m^2 on day 8 of CODOX-M$\pm$R and on day 4 of

(A) CODOX-M-R protocol

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Cyclophosphamide 800 mg/m² IV	x	x																
Doxorubicin 50 mg/m² IV	x																	
Vincristine 1·4 mg/m² IV	x							x										
Rituximab 375 mg/m² IV								x										
Leucovorin (until MTX <0·1 μmol/l)											x	x	x	x				
Cytarabine 50 mg IT	x		x															
Methotrexate 3000 mg/m² IV										x								
G-CSF													x	x	x	x	x	x

(B) IVAC-R protocol

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ifosfamide 1500 mg/m² IV	x	x	x	x	x													
Cytarabine 2000 mg/m² IV	x	x																
Mesna 375 mg/m² IV	x	x	x	x	x													
Etoposide 60 mg/m² IV	x	x	x	x	x													
Rituximab 375 mg/m² IV				x														
Methotrexate 12 mg IT						x												x
G-CSF							x	x	x	x	x	x	x	x	x	x	x	x

Fig 1. BC Cancer CODOX-M-R/IVAC-R protocol. (A). CODOX-M-R. (B) IVAC-R. G-CSF, granulocyte-colony stimulating factor; IT, intrathecal; IV, intravenous; m, metre; mg, milligram; MTX, methotrexate.

IVAC±R. Treatment was risk-adapted in that low-risk patients received Magrath A/B (CODOX-M±R/IVAC±R) plus one additional cycle of CODOX-M±R, while high risk patients received 2 full cycles of Magrath A/B. High-dose chemotherapy and SCT in first remission was considered in all eligible patients until 2010. Patients planned for a SCT in first remission received one cycle each of CODOX-M±R and IVAC±R before proceeding to total body irradiation (TBI) based conditioning, followed by autologous or allogenic transplant. The decision to proceed to autologous *versus* allogeneic transplant was at the physician's discretion depending on donor availability, degree of marrow involvement, and comorbidities.

Patients who were initiated on the Magrath regimen as first-line therapy for BL were included in this analysis. Patients who received pre-induction or debulking chemotherapy [such as single-agent cyclophosphamide or CVP (cyclophosphamide, vincristine, prednisone)/CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-like therapy] were also included. Treatment modifications were recorded and categorized as either need for pre-induction chemotherapy, dose modifications, omission of chemotherapeutic agents or change in chemotherapeutic agent.

Statistical analysis

Primary outcomes were OS, defined as time from diagnosis to last follow-up or death, and PFS, defined as time from diagnosis to progression, last follow-up or death. Survival was estimated using the Kaplan Meier method and compared using the log-rank test. When analysing survival outcomes, high and low-risk patients were combined to represent the overall risk-stratified approach of the protocol. Multivariate Cox proportional hazards regression was performed to evaluate the association between the following variables and survival outcomes: age >60 years, gender, Ann Arbor stage 3–4, Eastern Cooperative Oncology Group (ECOG) performance status 2–4, International Prognostic Index (IPI) score 4–5, elevated LDH, albumin >30 g/l, hemoglobin >100 g/l, bone marrow involvement, CNS involvement, bulk ≥5 cm, HIV positivity, rituximab incorporation, MTX incorporation, and SCT in first remission. Variables with $P < 0{\cdot}1$ (2-sided) in univariate analyses were entered into the multivariate logistic regression models. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for the survival comparisons. Stata version 11.0 (StataCorp, College Station, TX) was used to analyse data.

Results

Patient characteristics

Between 1 January 2001 and 31 December 2015, 81 patients diagnosed with BL and initiated on the modified Magrath regimen in BC were identified. Baseline characteristics are summarized in Table I. Briefly, 64 (79%) of patients were male and the median age was 47 years (range, 18–72). All patients had a *MYC* translocation on central pathology review. The majority of patients had high risk features including 66 patients (83%) with Ann Arbor stage 3–4 disease, 49 (62%) with B symptoms, 59 (74%) with elevated LDH, 53 (70%) with bulky disease and 54 (67%) with more than one extranodal site. Eighteen (22%) patients were HIV positive, 8 (11%) patients had CNS involvement at diagnosis,

Table I. Baseline patient characteristics ($N = 81$).

Baseline characteristics	*N* (%)
Male	64 (79)
Median age, years (range)	47 (range 18–72)
Age >60 years	16 (20)
MYC rearrangement	81 (100)
Confirmed t(8;14)	51 (63)
Ann Arbor stage 3–4 ($n = 80$)	66 (83)
B symptoms ($n = 79$)	49 (62)
ECOG performance status 2–4	31 (38)
>1 extranodal site	54 (67)
Elevated LDH ($n = 80$)	59 (74)
Bulk ≥5 cm ($n = 76$)	53 (70)
HIV positive	18 (22)
CNS involvement ($n = 74$)	8 (11)
BM involvement	31 (38)
IPI score 4–5 ($n = 79$)	31 (39)
BC Cancer High Risk	79 (98)

BM, bone marrow; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IPI, International Prognostic Score; LDH, lactate dehydrogenase; t, translocation.

*BC Cancer High Risk defined as individuals presenting with any of the following: Ann Arbor stage IV, bulk greater than or equal to 5 cm, LDH greater than upper limit of normal, BM involvement, and/or CNS involvement.

and 31 (38%) patients had bone marrow involvement. All except 2 patients were stratified as high risk per the BC Cancer criteria.

Treatment and outcomes

Treatment modifications were common in the cohort, with over half of patients (53%) requiring some type of modification. Modifications included need for pre-induction chemotherapy in 12 patients (15%), generally due to unconfirmed diagnosis or inability to tolerate the Magrath regimen at the time of diagnosis, dose modifications in 7 (9%), omission of chemotherapeutic agents in 30 (37%), and change in chemotherapeutic agents in 10 (12%). The need for treatment modifications rose to 88% in patients older than 60 years (Table II). MTX was administered in 66 (81%) patients, while rituximab was administered in all but 4 patients, all of whom were treated before 2004. A small proportion of patients received radiotherapy (9%). The median time from diagnosis to end of treatment response assessment was 3·9 months (range, 0·5–16·3 months). Sixteen patients underwent a consolidative SCT in first remission as part of first line therapy (13 autologous and 3 allogenic), all prior to 2010. Among SCT patients, 2 experienced systemic relapse at 3 and 6 months and died from lymphoma.

Median follow-up of living patients was 4·7 years (range, 0·4–12·3 years). Treatment outcomes by age are shown in Table II. Fifty-nine patients (77%) had a complete remission and 7 (9%) had a partial remission, for an overall response rate of 86%. Additionally, stable disease occurred in 4 patients (5%), while progressive disease occurred in 7 patients (9%). At last follow-up, 18 patients had relapsed or progressive disease, 17 of whom relapsed within the first year of diagnosis. One patient had a late relapse at 2·2 years from diagnosis. Sixteen patients died from relapse/progression while 1 patient was lost to follow-up shortly after receiving radiotherapy for a CNS relapse, and 1 patient remains in remission 4·2 years after an unrelated allogeneic SCT. This latter patient had a systemic relapse 5 months after completion of CODOX-M-R/IVAC-R ×2 cycles administered per protocol and entered a second CR with a repeat course of CODOX-M. One patient died from a secondary lung adenocarcinoma at 3·4 years after diagnosis. No treatment-related deaths were observed in this cohort of patients.

Survival outcomes

Survival outcomes for the entire cohort are shown in Fig 2. Two and 5-year PFS was 78% (95% CI: 68–86%) and 75% (95% CI: 63–83%) respectively, and 2 and 5-year OS was 81% (95% CI: 70–88%) and 77% (95% CI: 66–85%) respectively. Patients aged >60 years had significantly worse 5-year OS and PFS compared with those aged ≤60 years: OS 40% vs. 86% ($P = 0·002$); PFS 40% vs. 82% ($P = 0·005$) (Fig 3). Patients who were able to complete the full Magrath regimen per-protocol ($n = 38$) had excellent outcomes with 5-year PFS and OS of 86% (95% CI: 70–94%) and 92% (95% CI: 76–97%), respectively, compared with those who required treatment modifications, where PFS and OS were both 66% (PFS $P = 0·04$ and OS $P = 0·008$) (Fig 4). Achievement of a complete or partial response was associated with 5-year OS of 87% (95% CI: 75–93%), compared with 5-year OS of 12% (95% CI: 3–44%) for those who had stable or progressive disease ($P < 0·001$).

Univariate and multivariate analyses

In univariate analysis (Table III), age >60 years, IPI score of 4–5, elevated LDH, omission of MTX and omission of rituximab significantly predicted for both worse PFS and OS. BM involvement was a significant predictor for worse OS. Of note, SCT in first remission did not significantly impact survival outcomes on univariate analysis. In multivariate analysis (Table IV), age >60 years significantly predicted for worse PFS with HR 3·36 (95% CI: 1·24–9·15), $P = 0·018$, and OS with HR 4·03 (95% CI: 1·36–11·95), $P = 0·012$, after controlling for covariates. Methotrexate incorporation was associated with a lower likelihood of an event for both PFS and OS: HR 0·28 (95% CI: 0·10–0·78), $P = 0·015$ and HR 0·28 (95% CI: 0·09–0·85), $P = 0·025$, respectively. Similarly, rituximab incorporation was also associated with improved PFS and OS: HR 0·09 (95% CI: 0·02–0·37), $P = 0·001$, and HR 0·04 (95% CI: 0·08–0·24), $P < 0·001$, respectively, after controlling for covariates. Other variables that were significant on univariate analyses were shown not to be significant on multivariate analyses.

Table II. Treatment characteristics and outcomes.

Characteristic	Total (%) $n = 81$	Age ≤60 years (%) $n = 65$	Age >60 years (%) $n = 16$
Treatment modifications*	43 (53)	29 (45)	14 (88)
Pre-induction therapy	12 (15)	9 (14)	3 (19)
Dose modifications	7 (9)	2 (3)	5 (31)
Omission of agent	30 (37)	20 (31)	10 (63)
Change of agent	10 (12)	8 (12)	2 (13)
Rituximab received	77 (95)	62 (95)	15 (94)
Systemic MTX received	66 (81)	55 (86)	11 (69)
SCT in first remission	16 (20)	16 (13 auto, 3 allo)	0
Radiation treatment	7 (9)	4 (6)	3 (19)
End of treatment response ($n = 77$)			
Complete remission†	59 (77)	48 (77)	11 (73)
Partial remission	7 (9)	6 (10)	1 (7)
Stable disease	4 (5)	4 (6)	0 (0)
Progressive disease	7 (9)	4 (6)	3 (20)
Alive at last follow up	64 (79)	56 (86)	8 (50)
Relapse/progression	18 (22)	11 (17)	7 (44)
Cause of death			
Burkitt lymphoma	16 (20)	9 (14)	7 (44)
Secondary malignancy	1 (1)	0	1 (6)

MTX, methotrexate; SCT, stem cell transplant; auto, autologous; allo, allogeneic.

*Treatment modifications are not mutually exclusive.

†CR includes CRu in 9 and clinical CR in 13 (i.e. No end of treatment imaging, but resolution of all palpable disease and normalization of blood counts).

HIV positive patients

Patients who were HIV positive at the time of diagnosis were monitored for CD4 counts and viral load and continued on highly active antiretroviral therapy (HAART) as directed by the infectious disease team. In this study, we identified 18 patients who were HIV positive at the time of diagnosis, with 1 patient having confirmed CNS involvement. Of these 18 patients, 8 patients required various forms of treatment modifications, primarily omission of chemotherapeutic agents. In our HIV cohort, 2 patients relapsed (one systemic and one CNS relapse) while the remainder were in remission at a median follow-up of 3·7 years (range, 0·4–11·4 years). Five-year PFS was 88% and 5-year OS 94% in this subgroup, and these were not significantly different from the HIV-negative patients ($P = 0{\cdot}154$ for PFS and $P = 0{\cdot}083$ for OS).

Discussion

It has long been established that treatment of BL with intensive, multi-agent chemotherapy with aggressive CNS prophylaxis results in high cure rates, although no single regimen is considered standard of care. Evidence for different treatment regimens comes primarily from clinical trials and single-institution reports. There is a paucity of data regarding real-world outcomes of the various treatment regimens for BL, making it difficult to compare regimens against one another. This is particularly important now that new protocols, such as dose-adjusted EPOCH-R, are being evaluated in clinical trials and are making their way into clinical practice.

We have demonstrated in this large, population-based cohort of adult patients with BL that a risk-adapted, modified Magrath regimen resulted in an excellent long-term PFS of 77% and OS of 75%. OS and PFS significantly improved to over 80% for patients under 60 years of age and approached 90% for those who were able to complete the regimen per protocol. It is also notable that time from initiation of treatment to end of treatment response assessment was only a median of 3·9 months, making this regimen shorter than many alternate BL regimens. We did not observe any treatment-related deaths among our cohort.

Our results compare favourably to phase II trials reporting on outcomes with CODOX-M/IVAC. The 3 largest reports of CODOXM/IVAC include the initial report by Magrath *et al* (1996), which included 21 children and 20 adults aged less than 60 years with small non-cleaved NHL and demonstrated a 2-year EFS of 92%; however there was significant toxicity, including profound and disabling neurotoxicity, associated with this regimen (Magrath *et al*, 1996). The UK Lymphoma Group LY06 study included 52 HIV-negative patients under 60 years of age with BL or Burkitt-like lymphoma and confirmed the high cure rates with CODOXM/IVAC with a 2-year EFS of 65% and OS of 73% (Mead *et al*, 2002). Another prospective trial by the UK and Australasian groups (MRC/NCRI LY10 trial) examined a modified CODOX-M/IVAC regimen with reduced-dose MTX in 128

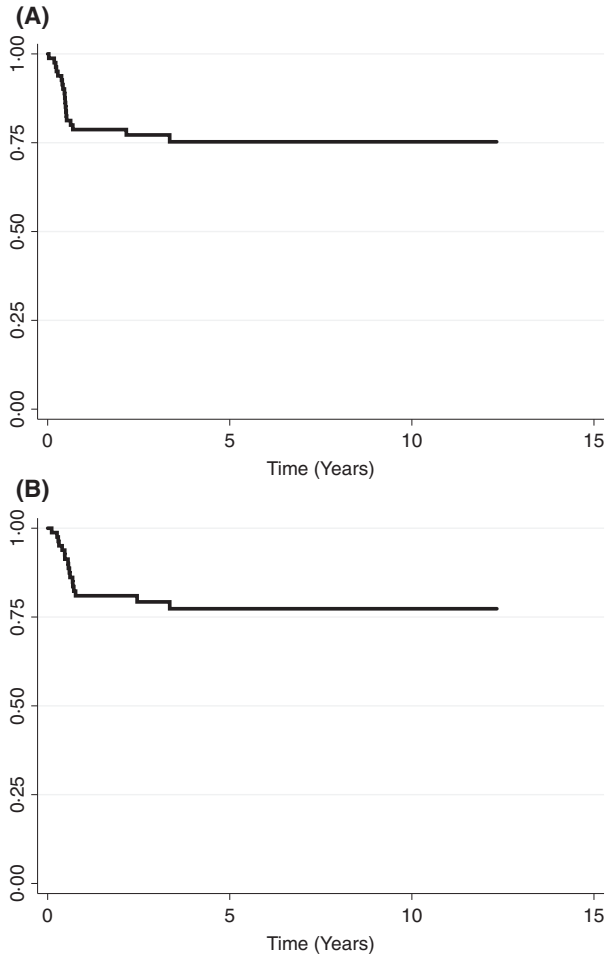

Fig 2. Survival outcomes for entire cohort of Burkitt lymphoma patients in British Columbia (n = 81). (A) Progression-free survival. (B) Overall survival.

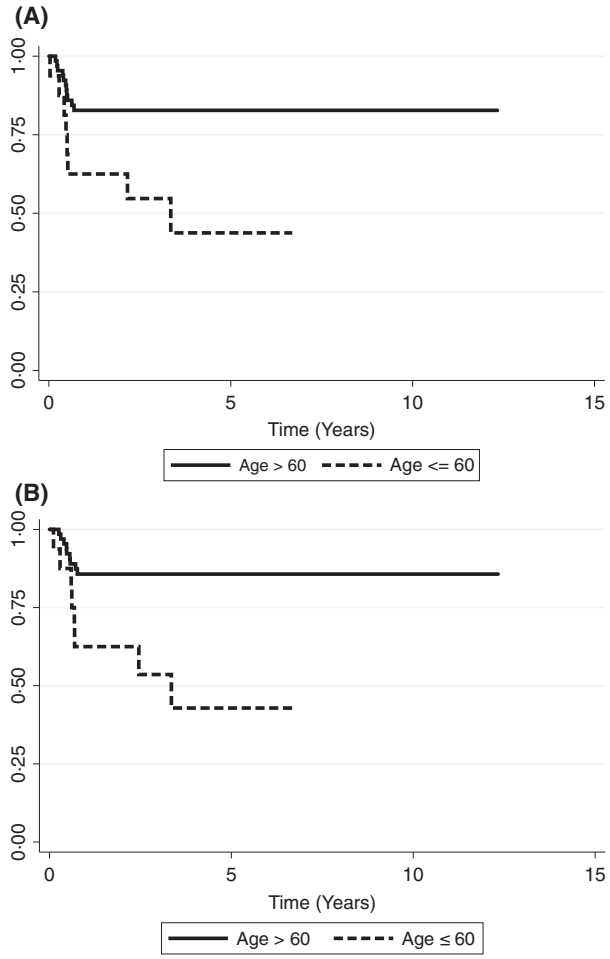

Fig 3. Survival outcomes for entire cohort of Burkitt lymphoma patients in British Columbia stratified by age ≤60 years (n = 65) and age >60 years (n = 16). (A) Progression-free survival. (B) Overall survival.

patients with aggressive B-cell NHL with Ki67 greater than 95%; 58 had BL and 70 had DLBCL (Mead *et al*, 2008). Further dose reductions of MTX, ifosfamide and cytarabine were planned for patients over 65 years of age. The 2-year PFS for the 58 patients with BL was 64%. In comparison to these trials, our report includes a more homogeneous population of patients with cytogenetically confirmed BL, with no age cut-off, and includes patients with HIV-associated BL.

Of the 18 patients who were HIV positive at the time of BL diagnosis, all remained on HAART throughout treatment with CODOX-M/IVAC±R. Their 5-year PFS and OS were both excellent, at 88% and 94%, respectively, and were not statistically different from the remainder of the cohort. The use of CODOX-M/IVAC±R among HIV-positive BL patients has been reported in previous studies, including a report from our group in combination with 3 other Canadian centres, involving 14 patients with HIV-associated BL treated with CODOX-M/IVAC±R, all of whom had acceptable toxicity and were alive at 11·2 months of follow-up (Rodrigo *et al*, 2012). A randomized phase II trial of dose-adjusted EPOCH-R conducted by the Acquired Immunodeficiency Syndrome Malignancies Consortium included 27 patients with HIV-associated BL and demonstrated the feasibility of EPOCH with concurrent R, with CR demonstrated in 73% of patients (Sparano *et al*, 2010). In a single-arm prospective trial of short-course EPOCH-R for three to six cycles (one cycle past CR) in HIV-positive BL patients, freedom from progression was 100% and OS 90% at a median follow-up of 73 months (Dunleavy *et al*, 2013). Although outcomes from this latter trial are excellent, the number of HIV-positive patients was small and no patients in this group had CNS involvement. One concern with the EPOCH-R regimen is the lack of systemic CNS-penetrating therapy, particularly in this subgroup of patients at high-risk of CNS disease.

Addition of rituximab to the modified CODOX-M/IVAC protocol became standard of care in BC as of 2004, which is reflected in our patient cohort, whereby 95% of patients received rituximab. Rituximab incorporation was associated with improved outcomes, consistent with previous clinical trials

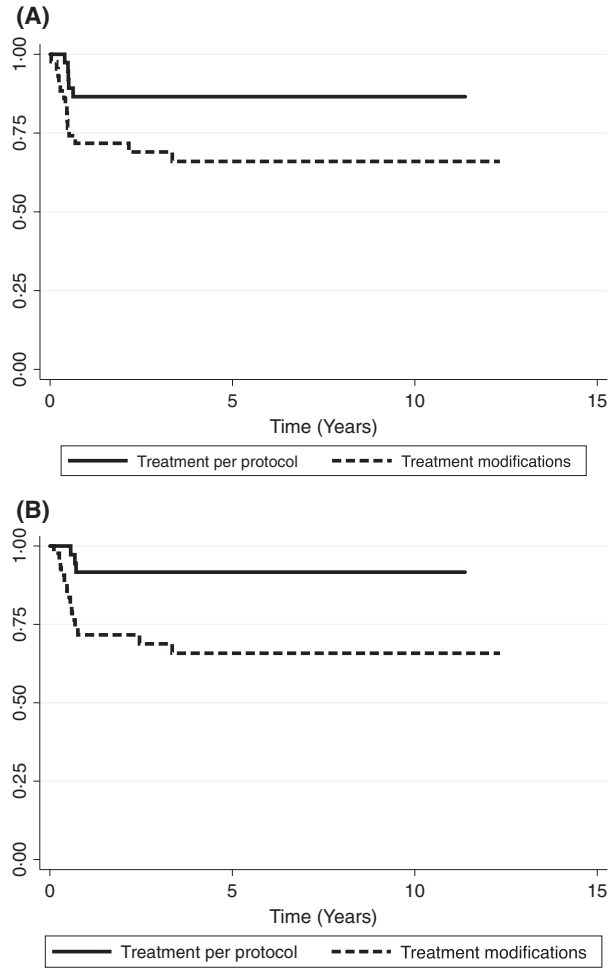

Fig 4. Survival outcomes for the entire cohort of Burkitt lymphoma patients in British Columbia stratified by patients who received treatment per protocol (n = 38) and patients who received treatment modifications (n = 43). (A) Progression-free survival. (B) Overall survival.

(Thomas *et al*, 2006; Evens *et al*, 2013; Hoelzer *et al*, 2014; Rizzieri *et al*, 2014; Ribrag *et al*, 2016); however numbers in the group without rituximab were small and results should be interpreted with caution. The largest prospective study of the addition of rituximab was a non-randomized multicentre trial from Germany involving 363 BL patients treated with rituximab in combination with short-duration intensive combination chemotherapy, in which 5-year OS and PFS were estimated at 80% and 71%, respectively (Hoelzer *et al*, 2014). A recently published phase 3 randomized trial by Ribrag *et al* (2016) demonstrated significantly improved outcomes with the addition of rituximab to the LMB regimen with 3-year EFS 75% vs. 62%.

High-dose chemotherapy and SCT in first remission was the standard of care in BC until 2010, when this practice was discontinued given the excellent results seen with CODOX-M/IVAC±R alone. Our analysis confirms that SCT in first remission was not associated with improved survival outcomes in our cohort. We currently reserve SCT for the rare patient with relapsed disease who is sensitive to salvage

Table III. Univariate analysis of predictors of progression-free survival and overall survival for the BL patient cohort.

Variable	PFS *P*-value	OS *P*-value
Age >60 years	0·005	0·002
Gender	0·967	0·777
Ann Arbor stage 3–4	0·723	0·452
ECOG performance status 2–4	0·340	0·175
IPI 4–5	0·001	0·001
Elevated LDH	0·017	0·027
BM involvement	0·098	0·035
CNS involvement	0·486	0·569
Bulk	0·196	0·332
HIV status	0·155	0·083
R incorporation	<0·001	<0·001
Systemic MTX incorporation	0·006	0·004
SCT in first remission	0·242	0·328

BL, Burkitt lymphoma; BM, bone marrow; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IPI, International Prognostic Score; LDH, lactate dehydrogenase; MTX, methotrexate; OS, overall survival; PFS, progression-free survival; R, Rituximab; SCT, stem cell transplant.

chemotherapy, and in fact the only long-term survivor after relapse in our cohort was a patient who successfully went on to receive an allogeneic SCT after response to second-line therapy. This approach is corroborated by other retrospective series examining the role of SCT in BL, including a report from the European Society for Blood and Marrow Transplantation where 3-year OS was 37% among patients transplanted in a chemosensitive relapse, compared to 7% for those with chemoresistant disease (Sweetenham *et al*, 1996). As expected, patients in our cohort who did not achieve a complete or partial remission after CODOX-M/IVAC±R had a dismal prognosis, with a long-term survival of only 12%.

Subgroup analysis of patients in our cohort who were aged >60 years demonstrated significantly worse outcomes both on univariate and multivariate analyses compared to those under age 60 years for both OS and PFS. While there may be many factors leading to this difference, one notable factor is that 14 of 16 patients (88%) over age 60 years required treatment modifications due to comorbidities or toxicity. We demonstrated that those requiring treatment modifications had significantly worse outcomes compared to those who were able to complete the regimen per protocol, with 5-year OS 66% vs. 92% (P = 0·008) and PFS 66% vs. 86%. We also demonstrated that omission of systemic MTX was associated with significantly worse PFS and OS in both univariate and multivariate analyses and again, systemic MTX omission was more frequent among patients aged >60 years. The MRC/NCRI LY10 study, which incorporated planned treatment modifications for patients aged >65 years, also demonstrated significantly inferior outcomes in this subgroup compared to those aged <65 years, with 2-year PFS 25% vs. 65%, HR 0·13 (P < 0·001) and 2-year OS 25% vs. 69%, HR 0·11, P < 0·001 (Mead *et al*, 2008).

Table IV. Multivariate analysis of predictors of overall and progression-free survival for BL patient cohort using Cox proportional hazards regression.

	Progression-free survival			Overall survival		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age >60 years	3·36	(1·24–9·15)	0·018*	4·03	(1·36–11·95)	0·012*
IPI score 4–5	2·85	(0·95–8·58)	0·063	3·51	(0·91–13·53)	0·069
Elevated LDH	3·25	(0·36–29·72)	0·296	2·00	(0·19–20·78)	0·561
BM involvement	1·22	(0·45–3·29)	0·451	1·55	(0·54–4·51)	0·417
HIV status	–	–	–	1·35	(0·14–12·81)	0·795
R incorporation	0·09	(0·02–0·37)	0·001*	0·04	(0·08–0·24)	<0·001*
MTX incorporation	0·28	(0·10–0·78)	0·015*	0·28	(0·09–0·85)	0·025*

BL, Burkitt lymphoma; BM, bone marrow; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; IPI, International Prognostic Score; LDH, lactate dehydrogenase; MTX, methotrexate; R, rituximab.
*$P < 0·05$, statistically significant.

While some regimens for BL have pre-phase chemotherapy built into the protocol (Ribrag *et al*, 2016), in BC, the use of pre-phase chemotherapy was left to the discretion of the treating physician. We demonstrated that a substantial number of patients were treated with the Magrath regimen without modifications (i.e. no pre-phase chemotherapy or dose modifications) and had excellent outcomes with 5-year OS 92% and PFS 86%; therefore, use of routine pre-phase chemotherapy with the modified Magrath regimen may not be required and rather could continue to be considered on a case by case basis.

This study has several limitations largely due to its retrospective nature. We therefore focused primarily on reliable endpoints including OS and PFS. The decision to treat with CODOX-M/IVAC±R was at the discretion of the treating physician and not subject to rigorous criteria, as in clinical trials. We were not able to collect detailed information on toxicity because reporting varied in this non-clinical trial setting. Response assessments may be inaccurate given that imaging was not mandatory for all patients, and documentation of response was not standardized. In addition, subgroup analyses should be interpreted with caution due to low numbers.

Despite these limitations, our analysis provides a benchmark for real-world outcomes of the CODOX-M/IVAC±R regimen for the treatment of non-HIV and HIV-associated adult BL. Long-term OS and PFS were 77% and 75% respectively when the entire population was considered, regardless of age and HIV status; this increased to 92% and 86% respectively for those able to tolerate the full regimen as planned. Based on these results, at our centre, adults aged >60 years with BL and those unable to tolerate a modified Magrath regimen per protocol are now considered for alternate regimens, such as dose-adjusted EPOCH-R, with limited data to report thus far. The CODOX-M/IVAC+R regimen, however, remains the standard of care for those able to tolerate it in full, given the excellent outcomes seen in this population.

Contribution

KYZ, KWS, JMC and ASG designed the research study; KYZ, KWS, JMC, HL, MJB, KR, YAM, DLF, DEH, SHN, SN, TJN, MMP, DSS, HJS, CLT, LHS, RB and ASG performed the research; KYZ and ASG analysed the data; KYZ, KWS, JMC, GWS and ASG interpreted the data. All authors contributed to the writing of the manuscript and reviewed and approved the final manuscript.

Conflict of interest disclosure

ASG, JMC, and LHS have received institutional research funding from Roche Canada.

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