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The use of anthracyclines in the treatment of endemic Burkitt lymphoma

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Summary

Burkitt lymphoma is the most common malignancy in children in Malawi, the world's poorest country, where there is a long history of treating this disease using a 28-day cyclophosphamide-based protocol. Stage III/IV disease has had poor outcomes. In an attempt to improve the outcome for higher stage disease, anthracyclines were added to the existing protocol. The disease-free (DFS) and overall survival (OS) of 58 children with cytologically confirmed Burkitt lymphoma admitted during 2012–2014 and treated using this protocol were calculated. Six (10%) children had stage I disease, ten (17%) stage II and 42 stage III or IV (73%). Overall 12-month DFS (OS) was 68·5% (72·9%); for stage I disease 100% (100%), stage II 56·2% (60%), stage III/IV 66·3% (72·2%). The DFS was significantly improved from the previous protocol ($P = 8 \times 10^{-4}$). The addition of doxorubicin to stage III and IV disease resulted in a markedly improved DFS. Anthracyclines are deliverable in resource-poor settings and possibly improve the survival of children with Burkitt lymphoma.

Keywords: Burkitt lymphoma, anthracyclines, resource-challenged countries, endemic, chemotherapy.

Endemic Burkitt lymphoma (BL) is the most common tumour in Malawian children, accounting for almost 50% of all childhood tumours. The frequency of this tumour in Malawi is associated with the presence of holoendemic malaria and the early acquisition of Epstein–Barr Virus (EBV). The mechanism is thought to involve the interaction of the malarial parasite and EBV-infected cells (Molyneux *et al*, 2012).

Endemic BL is very sensitive to chemotherapy, particularly cyclophosphamide, as well as intrathecal methotrexate for central nervous system disease (Nkrumah *et al*, 1985; Traoré *et al*, 2011; Magrath, 2012; Molyneux *et al*, 2012). Sporadic BL in resource-rich countries has a disease-free survival (DFS) greater than 90% even in advanced stage disease (Patte *et al*, 2007; Gerrard *et al*, 2008) but this requires very intensive chemotherapy, which is neither feasible nor safe in most low-income countries. As a result, countries, such as Malawi, which have previously tried simplified versions of the LMB protocols (B cell Non Hodgkin Lymphoma and B Acute Lymphoblastic Leukaemia schedules from the Société Française d'Oncologie Pédiatrique) with unacceptable toxicity, have developed protocols appropriate to their setting, both in terms of length of treatment and intensity (Hesseling *et al*, 2003, 2012; Depani *et al*, 2015). The modified LMB 89 protocol was a 77-day regimen with reduced doses of methotrexate (2 vs. 3 g/m^2), vincristine, 1·5 mg/m^2 vs. 2 mg/m$^{2;}$ adriamycin and etoposide were not included. No radiotherapy was available. Despite these reductions in

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chemotherapy and exclusions of Stage 4 disease and children with human immunodeficiency virus (HIV) infection, deaths during treatment were 23% and a further 23% abandoned treatment (Hesseling *et al*, 2003).

Using a range of protocols between 1997 and 2010 with a duration between 28 and 57 days, the DFS was approximately 50% for all stages but with an average event-free survival of approximately 30% for stage III and IV disease (Table I) (Hesseling *et al*, 2005, 2008a, 2009, 2012; Depani *et al*, 2015). The rescue rate at relapse has remained around 30% over this time (Hesseling *et al*, 2008b). During this period, the oncology unit at the Queen Elizabeth Central Hospital in Blantyre, Malawi has improved supportive care and introduced treatment protocols to treat several previously untreated cancers, such as acute lymphoblastic leukaemia (Chagaluka *et al*, 2013; Israëls *et al*, 2013a; Carey *et al*, 2014).

With this experience and the desire to improve the outcome of higher stage BL without an increase in the duration of stay for the families, doxorubicin at a total dose of

Table I. Comparative table of patient details and outcomes using Malawi protocols for treatment of Burkitt lymphoma.

	Malawi 1997 (Hesseling *et al*, 2003) a	Malawi 2000 (Hesseling *et al*, 2005) b	Malawi 2002 (Hesseling *et al*, 2008a) c	Malawi 2003 (Hesseling *et al*, 2008a) d	Malawi 2006 (Hesseling *et al*, 2009) e	Malawi 2010 (Depani *et al*, 2015) f	Malawi 2012–14 g
Total patients (*n*)	44	42	129	140	40	70	58
Patient characteristics							
Median age, years	7	7	7	6	7	8	7
Male:Female ratio	1·4	2·5	1·6	1·3	1·3	1·5	0·93
Malaria positive	23%	26%	+	+	17%	26%	13·2%
HIV positive	5% ł	2% ł	2%	+	2%	3%	3%
Malnourished	77%	67%	+	+	50%	60%	43%
Staging							
Stage I	17%	12%	6%	8%	3%	4%	10%
Stage II	9%	19%	18%	20%	22%	29%	17%
Stage III	50%	50%	50%	57%	60%	30%	73%
Stage IV	24%	19%	26%	15%	15%	37%	
Sites of disease							
Face	79%	74%	68%	70%	70%	64%	57%
Abdomen	61%	55%	74%	71%	70%	47%	48%
Paraplegia	3%	12%	11%	11%	15%	17%	10%
CSF	1%	5%	12%	+	15%	26%	16%
BM	17%	14%	16%	+	2·5%	9%	13%
Outcomes							
On-treatment deaths	23%	26%	8%	6%	2·5%	3%	12%
Absconded	23%	0%	1%	+	7·5%	3%	5%
CCR	89%	96%	74%	87%	88%	81%	82%
Rescue at Relapse	20%	29%	29%	23%	40%	29%	36%
Overall DFS	57%*	33%	50%*	57%*	48%	45%	70·6%
Stage I DFS	90%	50%	55%	+	100%	100%	100%
Stage II DFS	+	50%	53%	+	55%	83%	56%
Stage III DFS	52%	24%	48%	+	50%	24%	66·3%
Stage IV DFS	ł	25%	10%	+	17%	32%	
Stage III/IV DFS	+	24·3%	35%	+	43·4%	28·4%	66·3%

Ara-C, cytarabine; BM, bone marrow; CCR, complete clinical response; CPM, cyclophosphamide; CSF, cerebrospinal fluid; DFS, disease-free survival; HC, hydrocortisone; HIV, human immunodeficiency virus; IT, intrathecal; MTX, methotrexate; VCR, vincristine.

(a) Modified LMB89 group B protocol: doxorubicin omitted, dose reduction of iv MTX, CPM and Ara-C (b) IT MTX/HC + COP (CPM 300 mg/m^2; VCR 1 mg/m^2; prednisolone 60 mg/m^2) day 1 for Stage I/II; days 1,8 for Stage III/IV + COMP (CPM 500 mg/m^2; VCR 2 mg/m^2; iv MTX 2 g/m^2; prednisolone 60 mg/m^2) day 22 + CPM 40 mg/kg iv + IT MTX/HC 15 mg days 1,8 and 15 + CPM 40 mg/kg iv days 29, 43 and 57 for Stage III/IV (d) CPM 40 mg/kg (iv for first dose then po) + IT MTX/HC 12·5 mg days 1,8 and 15 + CPM 40 mg/kg po days 29, 43 and 57 for Stage III/IV (e) CPM 40 mg/kg day 1, CPM 60 mg/kg days 8, 18 and 28, IT MTX/HC 12·5 mg days 1, 8, 18 and 28 (f) CPM (40 mg/kg iv with maximum total dose of 1·6 g on day 1; 60 mg/kg po/iv with maximum total dose of 2·4 g on days 8, 18 and 28), prednisolone 60 mg/m^2/day in 2 divided doses days 1–5, VCR (1·5 mg/m^2 with maximum dose of 2 mg on days 1, 8, 18 and 28) and IT MTX (12·5 mg/dose) and IT HC (12 mg/dose) on days 1, 8, 18 and 28 (g) as per (f) with the addition of Doxorubicin (stage III and IV) days 15 and 28 and CPM dose 40 mg/kg on days 15, 28.

+ not reported. ł excluded from study.

*DFS for stages I–III only.

120 mg/m^2 was added to the previous protocol that was developed in 2010 (Depani *et al*, 2015) and administered during week two and four of the treatment protocol. This dose was thought to offer potential benefits with minimal risk of cardiotoxicity and is used in the majority of children at similar doses for the treatment of non-haematopoietic tumours. It was felt that, by adding this on Day 15 and Day 28, the risk of inducing tumour lysis syndrome was lessened.

Subjects and methods

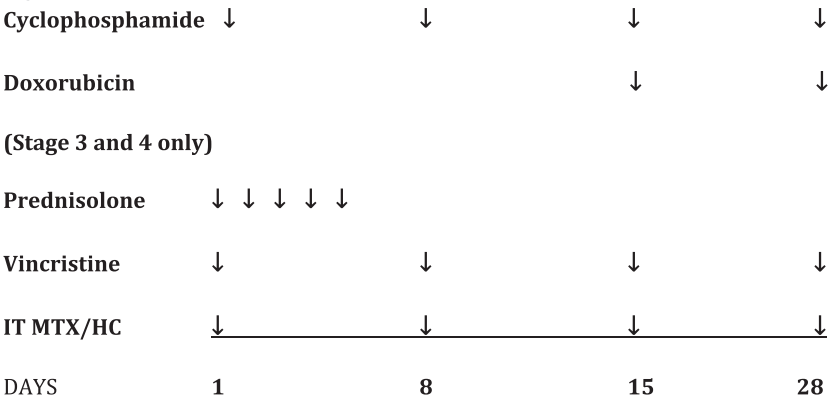
The Queen Elizabeth Central Hospital (QECH) is a large, public, government referral hospital in Blantyre, Malawi. The paediatric department admits 28 000 children a year, with 90 000 children seen in the emergency unit and outpatients departments. The paediatric oncology unit is a 23-bedded unit housed within the paediatric department and receives about 320 new patients a year.

Children between the ages of one and 16 years of age admitted to the oncology ward at the QECH (all patients aged 16 years or under with a suspected cancer diagnosis are admitted to the oncology ward) with a cytologically confirmed diagnosis of BL were included in this study. Informed consent was obtained from the patients/guardians prior to commencement of treatment.

Initial examination and investigations ~~on~~ all children with a clinical diagnosis of BL included recording of all tumour sites by clinical examination, ~~chest X ray~~ and abdominal ultrasound. Weight, height and mid-arm circumference were measured. Laboratory investigations included a full blood count, rapid HIV test, malaria test, stool and urine microscopy. Under ketamine sedation a fine needle aspirate (FNA) was taken from an accessible tumour site together with a bone marrow aspirate (BMA) and cerebrospinal fluid (CSF); (cytospin was not available). Slides of FNA, BMA and CSF were stained with Rapidiff stain kit (Clinical Service Laboratory, QECH) and photographs of the slides, using a Jenoptic camera (CT 13 with Prog Res Mac Capture Pro software) based on an Olympus microscope (CX31) were transmitted electronically for cytological diagnosis in Newcastle, UK by an experienced haematologist (Carey *et al*, 2014). The initial intrathecal chemotherapy was given at the time of the diagnostic lumbar puncture. Disease was staged according to the St Jude non-Hodgkin lymphoma staging system although it is appreciated that this is done without cross sectional imaging (Murphy, 1980). Due to the absence of some bone marrow and CSF results all stage III and IV tumours were analysed together to avoid inaccuracies of grading between the higher grades of tumour.

Patients were treated on a 28-day schedule (Malawi 2012–2014 protocol). Prednisolone 60 mg/m^2 was given orally in 2 divided doses on days 1–5; cyclophosphamide (40 mg/kg iv with maximum total dose of 1·6 g on days 1, 15 and 28; 60 mg/kg iv with maximum total dose of 2·4 g on day 8), vincristine (1·5 mg/m^2 with maximum dose of 2 mg on days 1, 8, 15 and 28), doxorubicin 60 mg/m^2 on days 15 and 28 (for stage III and IV disease only) and IT methotrexate (12·5 mg/dose) and hydrocortisone (12 mg/dose) on days 1, 8, 15 and 28 (Fig 1).

Appropriate supportive care was provided (Israels *et al*, 2013b) that included the following: hyperhydration and allopurinol during the induction chemotherapy with weekly full blood counts and delay of chemotherapy if the neutrophil count was <1·0 10^9/l, the patient was febrile or clinically unfit for treatment. Packed red cells were given if the haemoglobin fell below 50 g/l or for symptomatic anaemia. Platelets transfusions are not routinely available and were therefore not used. Nutritional supplementation in the form of a protein-rich supplement was given to all patients. Children who were febrile



Doses. Cyclophosphamide 40 mg/kg (max 1·6 g) days 1, 15, 22. 60 mg/kg (max 2·4 g) day 8
Doxorubicin 60 mg/m^2
Prednisolone 60 mg/m^2 per day in 2 divided doses
Vincristine 1·5 mg/m^2 (max 2 mg)
IT methotrexate 0-1 year: 6 mg, 1-2 years: 8 mg, 2-3 years: 10 mg, 3 + years: 12·5 mg

Fig 1. Treatment Schedule for higher stage Burkitt Lymphoma in Malawi. IT, intrathecal; MTX, methotrexate

and neutropenic were treated according to the local protocol (Israëls *et al*, 2009). Echocardiograms were not performed.

Children were kept in hospital for the duration of their 28-day treatment and discharged when clinically stable. Children were reviewed at two, six and 12 months from the start of treatment and attempts were made to trace children who failed to attend.

The primary endpoint was 1-year DFS. Events were death, disease progression or relapse. Response to treatment was assessed on day 28. Complete clinical response (CCR) was defined as the absence of any visible or palpable disease either clinically or on ultrasound examination. Partial response was >50% clinical reduction in tumour volume and a poor response/resistant disease was <50% clinical reduction. Patients who did not achieve CCR or who relapsed were offered rescue chemotherapy. Haematological and infectious side effects of treatment were graded according to the National Cancer Institute common toxicity criteria for adverse events (CTCAE v 4·0; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Disease-free survival was defined as time elapsed from diagnosis to first event, which was tumour recurrence or progression. OS was defined as time elapsed from diagnosis to death. Features with categorical outcomes were analysed using log-rank tests and Kaplan–-Meier plots. Binary and continuous features were tested using Cox Proportional Hazards models and tested to confirm proportionality of hazards. All statistical analyses were performed using R (v3.2.0) (https://cran.r-project.org/manuals.html).

Results

Eighty-four children were admitted with suspected BL between March 2012 and January 2014 (Fig 1). Sixteen were excluded from the analysis, six were treated on different protocols as it was clinically thought that they did not have BL and only on later cytological examination were found to have BL [this is in comparison with nine patients in the previous study using the protocol developed in 2010 (Depani *et al*, 2015)]; seven children were lost to follow up despite extensive efforts to trace them [compared with 8 in the previous study using the protocol developed in 2010 (Depani *et al*, 2015)] and three absconded during initial treatment [compared to 2 in the previous study (Depani *et al*, 2015)]. Of the remaining 68 children with cytological confirmation of BL, 10 died before the diagnosis was confirmed and consequently received no treatment. This relatively high number is thought to be partly due to the fact that more children are presenting very late from neighbouring Mozambique. Analysis was performed on the remaining 58 children who were treated on the Burkitt protocol and for whom follow-up data was available. The previous study using the protocol developed in 2010 (Depani *et al*, 2015) was used as a comparator and the analysis for this study was performed in the same way. No significant differences with regard to clinical parameters and early events or treatment completion rates were found between the 2 studies. (Table II).

The median age at presentation was 7 years (2·42–18) with a male: female ratio of 0·93:1. Median duration of symptoms was 30 days (4–180). Three patients (5%) were HIV reactive at diagnosis. Twenty-five (43%) children were malnourished [assessed by mid upper arm circumference (MUAC), weight for height and weight for age less than 3rd percentile on at least one parameter) at presentation. Malarial parasites were seen on a thick blood film at presentation in 7 (13·2%) children.

Using the St Jude staging classification (Murphy, 1980) 6 (10%) children had stage I disease, 10 (17%) stage II, and 42 stage III or IV (73%). Thirty-four of the 42 children with Stage III/IV disease presented with clinically palpable abdominal masses, the remaining 8 were staged on ultrasound alone or with positive CSF or bone marrow. The site of disease is described in Table II.

Table II. Comparative figures for the two most recent Malawi Burkitt protocols.

	2010 study (Depani *et al*, 2015)	2012–2014 study	*P* value
Confirmed Burkitt lymphoma	75	78	
No follow-up post-treatment	8	7	
Absconded	2	3	
Died on treatment	2	7	
Dead prior to treatment	5	10	
Completed treatment with follow-up	58	51	0·28
Stage			
1	3	6	
2	17	10	
3 + 4	40	42	0·07
Age (years)			
Median (range)	8 (3–16)	7 (2·4–18)	0·60
HIV Status			
Positive	2	3	
Negative	56	48	0·66
Site			
Face	36 (60%)	33 (57%)	
Abdomen	28 (47%)	28 (48%)	
Orbit	12 (20%)	13 (22%)	
Bone	4 (7%)	2 (3%)	
Limb	2 (3%)	1 (2%)	
Paraplegia	12 (20%)	6 (10%)	
CSF	18 (30%)	7 (13 not done)	
Bone marrow infiltration	6 (10%)	5 (19 not done)	

CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.
Continuous variables (age) were compared using student's *t* test. Categorical data were compared using chi-squared tests of association and Fisher's exact test.

Seven children (12%) died during treatment; all appeared to be septic at the time of death although only one blood culture was positive (salmonella typhi). Two of these children were HIV positive. Five children died during the first 2 weeks of treatment (four prior to doxorubicin) the remaining two in week four and just after completion of treatment but whilst still inpatients. None appeared to have progressive disease at the time of death. All seven children who died had stage III/IV disease. Six children with stage III/IV disease had their second dose of chemotherapy (day 8) delayed (3–13 days), five had their third dose of chemotherapy (day 15) delayed and the fourth dose of chemotherapy (day 28) was delayed in two children. Four children had CTCAE grade 3 and 5 grade 4 leucopenia prior to day 8 chemotherapy, seven had grade 3 and eight grade 4 prior to day 15 chemotherapy and seven had grade 3 and five grade 4 prior to their day 28 chemotherapy.

Of the 51 children who completed treatment 42 (82%) had a CCR to treatment, seven (14%) a poor response (<50%) and two (4%) had no response. The two children who had no response remain alive and disease-free, one had surgical removal of disease in her ovary (mainly necrotic with few viable cells) followed by two further courses of chemotherapy. The other child did not receive any more therapy and remains alive and well 12 months after diagnosis. A fine needle aspirate post-treatment showed mainly necrotic tissue.

The 12-month DFS was 68·5% [standard error (SE) ± 6·6%), and was 100% for stage I disease, 56·2% (SE ± 16·5%) for stage II and 66·3% (SE ± 8·0%) for stage III/IV (Fig 2). Overall survival (OS) at 12 months was 72·9% (SE ± 6·2%) and was 100% for stage I disease, 60% (SE ± 15·5%) for stage II and 72·2% (SE ± 7·5%) for stage III/IV (Fig 2).

Eleven (9%) children relapsed. One was stage I at relapse (survived), 3 were stage II (1 survived), 4 stage III (2 survived) and 3 stage IV (none survived). Time to relapse ranged from 2·0 to 7·1 months (median 5·0 months). Seven (64%) children subsequently died, six of their disease and one from presumed sepsis, the remaining four (36%) remain alive and disease-free. Children were treated on the Malawi relapse protocol, which includes cyclophosphamide and high dose (1 g/m^2 iv) methotrexate. Follow-up of the survivors was over a period of 4·1–23·8 months (median 13·1 months) with only one having follow-up of less than 11 months (4·1 months) and the majority being seen at their 1 year follow-up visit.

Univariate analysis showed that significant factors at presentation affecting DFS were pedal oedema [P = 0·02, hazard ratio (HR) 3·34, 95% confidence interval (CI) 1·17 and 9·5] and haemoglobin level (Hb) (P = 0·0008, HR 0·66, 95% CI 0·52 and 0·84). For OS, significant presenting factors were pedal oedema (P = 0·01, HR 4·49, 95% CI 1·53 and 13·2) and Hb (P = 0·003, HR 0·69, 95% CI 0·54 and 0·88). Paraplegia appeared not to be a significant prognostic factor in this study compared to the previous Malawian study although the number of patients were too small for meaningful analysis (Depani *et al*, 2015).

Discussion

The results from this protocol are very encouraging for all those working in areas where endemic BL is prevalent. The addition of doxorubicin to the 2010 Malawi protocol (Depani *et al*, 2015) for higher stage disease (stage III and IV) has resulted in an improved DFS from 28% to 66·3% ~~%~~ for stage III/IV disease (Fig 2). DFS for all patients has improved, from 45% to 72·2%. The improvement in OS was

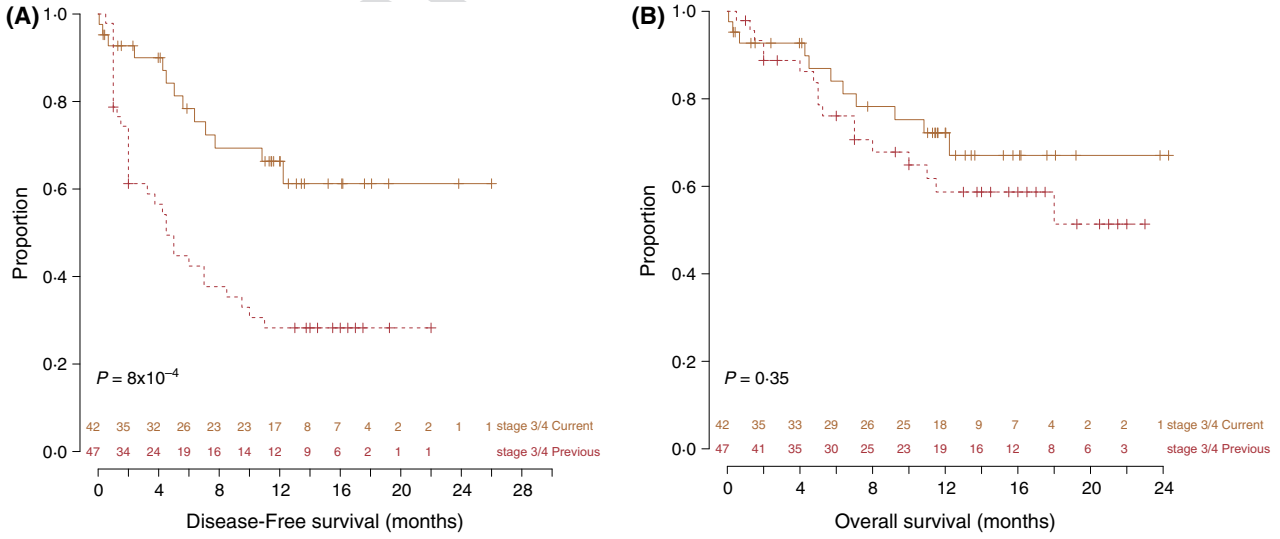


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Fig 2. Disease-free (A) and overall survival (B) for the current and previous (Depani *et al*, 2015) studies. Kaplan–Meier plot shows proportion surviving for each disease stage. At-risk tables are shown. *P*-values, assessed by log-rank test are shown for each plot.

not statistically significant although a trend was seen. This is probably due to the fact that seven children died of presumed sepsis during initial therapy (four prior to doxorubicin) which is five more than the previous study (one died in week 1 and one in week 2) (Depani *et al*, 2015). In keeping with the increase in death rate prior to treatment, this is suggestive that late presentation and poor condition prior to treatment is more likely to be the reason for these early deaths. In addition, the majority of early deaths were prior to the administration of doxorubicin. The increase in early mortality from presumed sepsis is therefore unlikely to be solely due to the addition of doxorubicin. The one-year DFS is a recognised end point for endemic BL and was reinforced by this study with a median time to relapse of 5 months, and the latest relapse occurring at 7·1 months (Hesseling *et al*, 2005; Magrath, 2012; Molyneux *et al*, 2012).

Other potential reasons for this improved outcome have been investigated. The study population, apart from the male to female ratio of nearly 1:1 in this study compared to 1·3–1·5, is comparable to that seen in other studies in similar settings (Hesseling *et al*, 2003, 2005, 2008a, 2009, 2012; Depani *et al*, 2015). The comparative numbers given in Table I suggest that HIV status, presence of malaria at diagnosis, rate of malnutrition at diagnosis, median age at presentation and site of disease were all within the expected range. Analysis of patients was performed in the same way as the previous studies (Hesseling *et al*, 2003, 2005, 2008a, 2009; Depani *et al*, 2015) to ensure that the improvement in outcome was not a result of bias in the analysis. Importantly, there was no statistical difference between the patients in the two studies. (Table II).

There was an increase in the number of children dying during treatment, mainly due to presumed sepsis [12% vs. 3–6% in the previous three studies (Hesseling *et al*, 2008a, 2009; Depani *et al*, 2015)]. This may have been partly due to the increased toxicity following the use of anthracyclines, resulting in an increased incidence of sepsis. Doxorubicin is used in the treatment of the majority of tumours other than BL (Israëls *et al*, 2013a; Carey *et al*, 2014) but, in the context of a rapidly growing tumour, increased vigilance is needed. The International Society of Paediatric Oncology– Paediatric Oncology in Developing Countries (SIOP PODC) supportive guidelines (Israels *et al*, 2013b) were followed. Pedal oedema was found to be a significant risk factor in determining survival and it is postulated that this is a surrogate marker for malnutrition.

The overall incidence of HIV infection in Malawian children is 3% (UNAIDS, 2014) and in the present study only three children who presented with BL had concurrent infection. All three of these children died of BL, one within a few days of treatment starting, one in week 3 of treatment and one at 4 months post-treatment.

These results are amongst the best in Sub-Saharan Africa and may show an improvement from studies in countries such as Cameroon, particularly for stage III/IV disease, of 27% vs. 66·3% (Hesseling *et al*, 2008a, 2012; Orem *et al*, 2011). These results need verification in a separate study before being widely recommended. Although the outcome of children in resource-rich countries with sporadic BL is above 90% (Patte *et al*, 2007; Gerrard *et al*, 2008), this is achieved with high intensity treatment and sophisticated supportive care, which is not possible in the resource-challenged world. An attempt to use intensive anthracycline-based treatment [CHOP (cyclophosphamide, doxorubicin, vincristine, predsisone) × 6] in Lilongwe, Malawi resulted in a toxic death rate of 40% and OS of 29% and is a useful reminder that using risk-adapted protocols is necessary in low income settings (Stanley *et al*, 2016). However the team in Blantyre has shown that, with dedicated and informed medical and nursing teams, even the world's poorest countries can make significant improvements to survival in some childhood tumours.

Caution should be used when using historical controls due to often-unquantifiable changes, such as supportive care, experience of staff in treating a particular disease and changes in demographics. However, in this study there were no major supportive changes from the last treatment protocol that would explain the difference.

Future treatment options to further improve the outcome are under consideration. These include the use of high dose methotrexate (1 g/m^2) during initial treatment or the use of agents such as rituximab. The dose of methotrexate is limited by the inability to measure methotrexate levels. Without the ability to measure methotrexate levels in Malawi, higher doses are deemed unsafe to deliver. Rituximab is both effective and tolerable in the majority of settings, but its use is limited by its cost in resource-poor settings. Should rituximab be affordable either by cost reduction or by demonstrating efficacy in smaller doses then this would be likely to become an important agent in improving survival for children with BL in low and middle income countries. Any increase in treatment intensity must be balanced against the ability of the children and their families to cope with the treatment, physically as well as being able to spend more time in hospital away from their familial responsibilities. Any increase in treatment intensity must also be supported by improvements in supportive care.

Anthracyclines used in treatment of endemic BL may improve the outcome of this disease. Further studies in other countries should be performed to confirm this result.

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Author contributions

Elizabeth Molyneux: Study design, data collection, data interpretation, writing. Ed Schwalbe: Data analysis and data interpretation, writing, figures. George Chagaluka: Data collection, study design. Kondwani Banda: Data collection. Trijn Israels: Data collection, study design. Sarita Depani: Data collection, analysis. Kirstin Mittermayer-Vassallo: Data collection. Kevin Windebank: Study design. Jessie Mvula: Data collection. Jenala Njiram'madzi: Data Collection. Stephen O'Brien: Data analysis, writing. Peter Carey: Data collection, data analysis, study design. Simon Bailey: Study design, data collection, data analysis, data interpretation, writing, figures.

Conflict of Interest

The authors have no conflict of interests to declare.

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