

An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study

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Background: Burkitt's lymphoma (BL) is a rare and rapidly progressive form of B-cell non-Hodgkin's lymphoma. Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC) is a highly effective alternating non-cross-resistant regimen developed by Magrath et al. (Magrath I., Adde M., Shad A. et al. *J Clin Oncol* 1996; 14: 925–934) at the US National Cancer Institute. The aim was to confirm these results in a larger, international, multi-centre study using International Prognostic Index-based criteria to assign prognostic groups, whilst slightly simplifying the protocol.

Patients and methods: A phase II study where: (i) low risk (LR) patients were treated with three cycles of modified CODOX-M; and (ii) high risk (HR) patients received treatment with four cycles of alternating modified CODOX-M and IVAC chemotherapy. Target of 60 patients, fit for protocol treatment, from 16 to 60 years of age with locally diagnosed, non-HIV-related, non-organ-transplant-related BL.

Results: Results are given for 52 of 72 registered patients whose pathological eligibility was confirmed by central pathology review: 12 LR plus 40 HR. The majority of patients ($n = 41$) completed protocol treatment, but toxicity was severe, especially myelosuppression and mucositis. Overall, 2-year event-free survival (EFS) was 64.6% (95% CI 50.4% to 78.9%) and 2-year overall survival (OS) was 72.8% (95% CI 59.4% to 86.3%). For LR, 2-year EFS was 83.3% and OS was 81.5%. For HR, 2-year EFS was 59.5% and OS was 69.9%.

Conclusions: This study confirms high cure rates with this CODOX-M/IVAC approach.

Key words: Burkitt's lymphoma, chemotherapy, CODOX-M, IVAC

Introduction

Burkitt's lymphoma (BL) is a rare and rapidly progressive form of B-cell non-Hodgkin's lymphoma (NHL) that most commonly occurs in males during childhood and young adult life [1–3]. Burkitt's lymphoma has a distinctive pathological appearance associated with an 8:14 translocation which

results in over-expression of *c-myc*; these changes promote mitosis such that virtually 100% of tumour cells are in cycle.

Burkitt-like lymphoma (B-LL) is a pathologically less well-defined lymphoma sub-type that is sometimes described as being associated with additional chromosomal translocations [1, 2, 4–8]. In the recent World Health Organization (WHO) Classification of Neoplasms of the Lymphoid System, B-LL has been identified as a sub-type of Burkitt's lymphoma [2].

Historically BL and B-LL have been treated together as diffuse small non-cleaved lymphoma according to the Working Formulation Classification [9]. In recent years, it has been increasingly recognised that cure [event-free survival (EFS) ≥ 1 year] is possible in a large majority of these neoplasms if

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appropriate intensive (although relatively brief) intravenous chemotherapy is given supplemented by intrathecal drugs. Whilst these results were initially described in paediatric series [10–18], recent series suggest that young adults can achieve similar results [19–25].

Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC) is an alternating non-cross-resistant regimen developed at the National Cancer Institute. The treatment of 20 adults and 21 children with small, non-cleaved NHL achieved an overall 92% 2-year EFS rate (100% in adults) [26]. It was decided to attempt to confirm these results in BL, a more precisely defined neoplasm. This larger study [United Kingdom Lymphoma Group (UKLG) LY06] planned to use International Prognostic Index (IPI)-based criteria [27] to divide patients into prognostic groups, whilst simplifying the protocol in view of previous vincristine-related neuropathy.

Patients and methods

Study design

This prospective phase II study was initiated by the UKLG, co-ordinated by the UK Medical Research Council's Clinical Trials Unit (CTU), London and funded by the Cancer Research Campaign. Clinicians from the UK, Poland, the Australasian Leukaemia and Lymphoma Group (ALLG) and Italy participated.

Registration entry criteria were broad in order to be as inclusive as possible. Eligible patients were aged from 16 to 60 years with non-HIV, non-organ-transplant-related BL, not previously treated with chemotherapy or radiotherapy and considered sufficiently physiologically and psychologically fit to receive the treatment protocol. Patients with severe organ dysfunction related to this diagnosis (most commonly acute renal failure) were eligible and were permitted to receive a single cycle of pre-induction low-dose chemotherapy [e.g. 50% dose cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)] to improve their clinical condition.

Appropriate ethical approval was gained for each centre, informed consent was obtained and the trial adhered to the Declaration of Helsinki.

Following a diagnosis of BL from the local pathologist, patients were evaluated urgently by physical examination with assessment of WHO performance status and measurement of tumour diameters. Blood was obtained for complete blood cell count (cbc), biochemical profile, lactate dehydrogenase (LDH) and urate levels. In addition, a chest X-ray, computed tomography of the chest, abdomen and pelvis, and bone scanning were performed. Bone marrow aspirate and trephine were obtained and a diagnostic lumbar puncture performed with instillation of intrathecal cytarabine.

After investigation an Ann Arbor stage was obtained. Patients were then allocated to a risk group on the basis of the age-adjusted prognostic index modified by allocation of patients with bulky disease to the high risk (HR) group. Thus, those patients with *all* of the following features were regarded as low risk (LR): (i) normal LDH level; (ii) WHO performance status of 0 or 1; (iii) Ann Arbor stage I–II; and (iv) no tumour mass ≥ 10 cm. All remaining patients were considered HR.

Patients were registered by contacting the CTU or ALLG, who subsequently collected all data. Analyses were performed at the CTU.

Treatment

Prior to chemotherapy, patients commenced oral allopurinol followed by intensive intravenous hydration; a standard anti-tumour lysis protocol was initiated.

Low risk patients were treated with three cycles of modified CODOX-M (protocol A); HR patients received treatment with four cycles of alternating modified CODOX-M and IVAC chemotherapy (protocol B) [26].

Therefore, all patients commenced protocol treatment with CODOX-M (Table 1). Prior to the administration of high-dose methotrexate, creatinine clearance had to be >50 ml/min (24-h urine collection or radioisotope technique). Methotrexate was administered regardless of cbc. The infusion was discontinued at 24 h regardless of the dose given. Leucovorin commenced 36 h after starting methotrexate infusion and continued until the serum methotrexate level was $<5 \times 10^{-8}$ M. Filgrastim $5 \mu\text{g}/\text{kg}$ (or $1 \times 263 \mu\text{g}$ ampoule) was given sub-cutaneously from day 13 until the absolute granulocyte count was $>1 \times 10^9/\text{l}$, when it was discontinued.

The second cycle was CODOX-M for LR patients and IVAC (Table 2) for HR patients. This, and subsequent cycles, commenced the day that absolute granulocyte count without growth factor support was $>1 \times 10^9/\text{l}$ with an unsupported platelet count of $>75 \times 10^9/\text{l}$. No dose modifications were recommended based on the previous cycle's degree or duration of myelosuppression, but vincristine was omitted in the presence of motor weakness, or the dose reduced to 1 mg in the presence of severe sensory symptoms.

All patients received CNS prophylaxis with high-dose intravenous methotrexate (LR and HR) and intravenous cytarabine (HR only) supplemented by intrathecal cytarabine and methotrexate. Patients with proven CNS disease received intensified treatment with intrathecal cytarabine 70 mg (or 15 mg if given via an Ommaya reservoir) on days 1, 3 and 5 of CODOX-M (cycle 1) and days 7 and 9 of IVAC (cycle 2) supplemented by intrathecal methotrexate 12.5 mg (2 mg if given via an Ommaya reservoir) on days 15 and 17 of CODOX-M (cycle 1) and day 5 of IVAC (cycle 2). For cycles 3 and 4 (HR patients only), the intrathecal drug dosing reverted to that shown in Tables 1 and 2.

Evaluation of response

The primary end point was EFS, defined as progressive disease at any time or death from any cause. Overall survival (OS) was an important secondary endpoint. Additionally, patients were evaluated for response using conventional criteria. Formal response evaluation took place 3–4 weeks following the final chemotherapy administration. Complete remission (CR) was defined as complete resolution of all evidence of lymphoma both clinically and radiologically. Partial remission (PR) implied a $>50\%$ reduction in the sum of the product of the perpendicular diameters of all measurable lesions. Progressive disease implied $>25\%$ increase in the size of lesions as defined for PR. All remaining patients had no response (NR). It was recommended that, following restaging, patients received follow-up monthly for 4 months, then two monthly for 1 year, with decreasing follow-up thereafter. After initial response evaluation, no routine follow-up CT scans were recommended.

Pathology review

Sections from all cases were to be reviewed centrally. Slides were stained by haematoxylin–eosin (H&E) and Giemsa techniques, and using the Ki-67 proliferation antigen. A diagnosis of BL was accepted when characteristic morphology was present together with 100% nuclear labelling on Ki-67 stained slides [2]. During the course of this study, the category B-LL was not accepted since this was not precisely defined and was liable to subjective interpretation. No routine cytogenetics were performed on tissue samples, as these were not routinely available at the time the protocol was written.

Table 1. Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M) regimen^a

Day	Drug	Dose	Method	Time
1	Cyclophosphamide	800 mg/m ²	i.v.	
	Vincristine	1.5 mg/m ² (max 2 mg)	i.v.	
	Doxorubicin	40 mg/m ²	i.v.	
	Cytarabine	70 mg	i.t.	
2–5	Cyclophosphamide	200 mg/m ²	i.v.	Daily
3	Cytarabine	70 mg	i.t.	
8	Vincristine	1.5 mg/m ² (max 2 mg)	i.v.	
10	Methotrexate ^b	1200 mg/m ²	i.v.	Over 1 h
		240 mg/m ²	i.v.	Each hour over 23 h
11	Leucovorin ^c	192 mg/m ²	i.v.	At hour 36
		12 mg/m ²	i.v.	Every 6 h until methotrexate level is $<5 \times 10^{-8}$ M
13	G-CSF ^d	5 µg/kg (or 1 × 263 µg ampoule)	s.c.	Daily until AGC $>1 \times 10^9/l$
15	Methotrexate	12 mg	i.t.	
16	Leucovorin	15 mg	p.o.	24 h after IT methotrexate

Commence next cycle on the day that unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.

^aThis differs from the NCI 89-C-41 protocol only by the omission of an injection of vincristine (1.5 mg/m²) on day 15 [26].

^bMethotrexate: methotrexate should only be given in the presence of normal serum creatinine for the patient's age and a measured creatinine clearance of >50 ml/min. Commence methotrexate regardless of blood counts. Stop infusion at hour 24 regardless of dose given.

^cLeucovorin: commence leucovorin at 36 h from start of methotrexate infusion. Continue leucovorin until the serum methotrexate level is $<5 \times 10^{-8}$ M. Leucovorin may be given orally after the first 24 h if patients are compliant, not vomiting and otherwise without complication.

^dG-CSF: 5 µg/kg (1 × 263 µg ampoule) s.c. daily until absolute granulocyte count is $\geq 1 \times 10^9/l$. Discontinue G-CSF at this time.

AGC, absolute granulocyte count; G-CSF, granulocyte colony-stimulating factor; i.t., intrathecal; i.v., intravenous; p.o., by mouth; s.c., subcutaneous.

Table 2. Ifosfamide, etoposide and high-dose cytarabine (IVAC) regimen^a

Day	Drug	Dose	Method	Time
1–5	Etoposide ^b	60 mg/m ²	i.v.	Daily over 1 h
	Ifosfamide	1500 mg/m ²	i.v.	Daily over 1 h
	Mesna	360 mg/m ² (mixed with ifosfamide) then 360 mg/m ²	i.v.	Over 1 h 3 hourly (seven doses/24 h period)
1 and 2	Cytarabine	2 g/m ²	i.v.	Over 3 hours, 12 hourly (total of four doses)
5	Methotrexate	12 mg	i.t.	
6	Leucovorin	15 mg	p.o.	24 h after i.t. methotrexate
7	G-CSF	5 µg/kg (or 1 × 263 µg ampoule)	s.c.	Daily until AGC $>1.0 \times 10^9/l$

Commence next cycle (CODOX-M) on the day that the unsupported absolute granulocyte count is $>1.0 \times 10^9/l$, with an unsupported platelet count of $>75 \times 10^9/l$.

^aThis does not differ from the NCI 89-C-41 protocol.

^bEtoposide given in 500 ml of normal saline or 5% dextrose.

AGC, absolute granulocyte count; i.t., intrathecal; i.v., intravenous; p.o., by mouth; s.c., subcutaneous.

Statistical considerations

A sample size of ~60 patients meeting all the eligibility criteria, and having a diagnosis of BL confirmed on independent pathological review, was planned. Equal numbers of LR and HR patients were anticipated. This number should generate sufficient events to allow 2-year EFS rate estimation with standard error $<7\%$.

Event-free survival and OS rates are displayed using Kaplan–Meier curves with time starting from the date protocol chemotherapy began. Estimates of EFS at a given time are displayed as a point estimate with the 95% confidence interval (CI) in parentheses. Exploratory analyses of a limited number of potential prognostic factors were carried out in which EFS rates were compared using the log-rank test; where categories were ordered, the log-rank test for linear trend was used.

Results

Accrual and eligibility

The study accrued from October 1995 to June 1999. Patients were registered by 45 consultants at 39 centres (range 1–20 patients; median 1). Because of the need to initiate protocol treatment rapidly, it was made possible to register patients after the start of chemotherapy. Of 72 patients registered for the trial, 18 (25%) were registered on or before the first day of chemotherapy, 42 (58%) within 7 days of starting chemotherapy and the remaining 12 (17%) were registered before completing cycle 1.

Sufficient histological material for the essential independent central pathological review was available in 65 of 72 patients: a diagnosis of BL was confirmed in 52 (80%) cases. The remaining patients ($n = 13$) were diagnosed on review as cases of diffuse large B-cell lymphoma (DLBCL). Overall, central pathology review disagreed with the local diagnosis in 20% of registered cases. The results presented here are for this core group of 52 eligible BL patients.

Patient characteristics

Baseline characteristics are shown in Table 3. Twelve LR patients were included: all IPI = 0. The primary site included Waldeyer's ring ($n = 4$), small bowel ($n = 2$), stomach ($n = 1$), chest ($n = 1$), nasopharynx ($n = 1$) and peripheral lymph node sites ($n = 3$). Forty HR patients were included. Four patients (10%) were IPI = 0, but assigned the HR protocol based on bulk disease. Disease was usually widespread at presentation; however, the most common primary sites identified were ileocaecal (nine patients, 23%) and bone marrow (five patients, 13%). Sixteen HR cases (40%) had bone marrow involvement from aspirate and/or trephine; 34 (85%) underwent evaluation of cerebrospinal fluid (CSF) for cytological involvement with lymphoma after lumbar puncture with three reporting positive. Four other HR patients were reported as having CNS involvement, including two cranial nerve palsies (one CSF positive, one not tested), one extra-dural mass and one with CSF-positive, cranial nerve palsy and an extra-dural mass. There were no cases of intra-cerebral mass. Twenty-six cases (65%) were Ann Arbor stage IV.

Treatment

Low risk

Eleven patients (92%) completed the planned three cycles of CODOX-M. The remaining patient suffered a toxic death after two cycles. Five patients (42%) had all three cycles at full dose. The drug most often reduced in the remaining patients was methotrexate. The median cycle 1–2 interval was 22 days (range 18–32) and cycle 2–3 was also 22 days (range 16–54).

High risk

Thirty patients (75%) completed the protocol-specified four cycles of alternating CODOX-M/IVAC; five patients (13%) received three cycles (reasons for stopping: one fatal disease progression, one toxic death and one fatality recorded as progression and toxicity; one excess toxicity and one patient changed treatment following local pathology revision to acute lymphoblastic leukaemia—central pathology review disagreed); three patients (8%) received two cycles (one fatal disease progression, one toxic death and one stopped protocol treatment following small bowel perforation with development of multiple intra-abdominal collections of pus) and two patients (5%) received one cycle (one toxic death, one fatality from disease and toxicity).

Seventeen patients (43%) received all four cycles without a reported reduction from protocol-specified dose. The most commonly reduced drug was methotrexate during CODOX-M and cytarabine (IV) during IVAC. The median cycle 1–2 interval was 24.5 days (range 16–40), cycle 2–3 was 20 days (range 14–41) and cycle 3–4 was 27 days (range 18–41).

Toxicities

Toxicity was severe for all patients. All had WHO grade 3/4 white blood cell count toxicities and nearly all had WHO grade 3/4 granulocyte toxicity. Figures 1 and 2 show the worst toxicity grade experienced. During the entire treatment protocol, LR patients required 0–25 (median 0) platelet units and 0–32 days (median 17) of treatment with i.v. antibiotics. High risk patients required 0–90 (median 8.5) platelet units and 0–67 days (median 19) antibiotics during chemotherapy. The majority of patients on each regimen required blood product support, especially HR patients; this may simply reflect that they received more cycles of chemotherapy.

There was little evidence of late toxicity during follow-up: one HR patient reported grade 3 neuropathy 3 months after relapsing, relapse having occurred 4 months after completing trial treatment. With regard to long-term fecundity: of 14 female patients aged <50 years at registration, three (one LR, two HR) have subsequently reported a pregnancy; there have been no reports of fatherhood amongst trial patients.

Response and survival

All BL patients (LR and HR)

Combining the results for the 52 LR and HR BL patients represents the overall risk-stratified approach of the protocol. Forty patients (76.5%; 95% CI 64.8% to 88.1%) attained CR and five attained PR. Overall 1-year EFS was 69.2% (95% CI 56.5% to 81.9%) and 2-year EFS 64.6% (95% CI 50.4% to 78.9%); 1-year OS was 75.0% (95% CI 63.1% to 86.8%) and 2-year OS 72.8% (95% CI 59.4% to 86.3%). Figure 3 shows EFS and OS for all 52 BL patients, combined.

Table 3. Baseline characteristics of patients (*n* = 52)

	Low risk		High risk		Total	
	Count	%	Count	%	Count	%
Age (years)						
<21	4	33	5	13	9	17
21–30	3	25	7	18	10	19
31–40	2	17	9	23	11	21
41–50	1	8	7	18	8	15
>50	2	17	12	30	14	27
Median	26.5		38.0		35.0	
Min–max	15–52		16–60		15–60	
Sex						
Male	10	83	20	50	30	58
Female	2	17	20	50	22	42
WHO performance status						
0	10	83	11	28	21	41
1	2	17	9	23	11	22
2	0	0	13	33	13	25
3	0	0	5	13	5	10
4	0	0	1	3	1	2
Missing	0	–	1	–	1	–
Ann Arbor Stage						
I	8	67	3	8	11	22
II	4	33	5	13	9	18
III	0	0	5	13	5	10
IV	0	0	26	67	26	51
Missing	0	–	1	–	1	–
Largest tumour mass						
<10 cm diameter	12	100	18	46	30	59
≥10 cm diameter	0	0	21	54	21	41
Missing	0	–	1	–	1	–
Lactate dehydrogenase (LDH)						
Normal	12	100	7	18	19	37
Raised	0	0	33	83	33	63
International Prognostic Index score (age-adjusted)						
0	12	100	4	10	16	31
1	0	0	2	5	2	4
2	0	0	19	48	19	37
3	0	0	14	35	14	27
Missing	0	0	1	3	1	2
Total	12	100	40	100	52	100

Due to rounding, percentages may not sum to 100%.

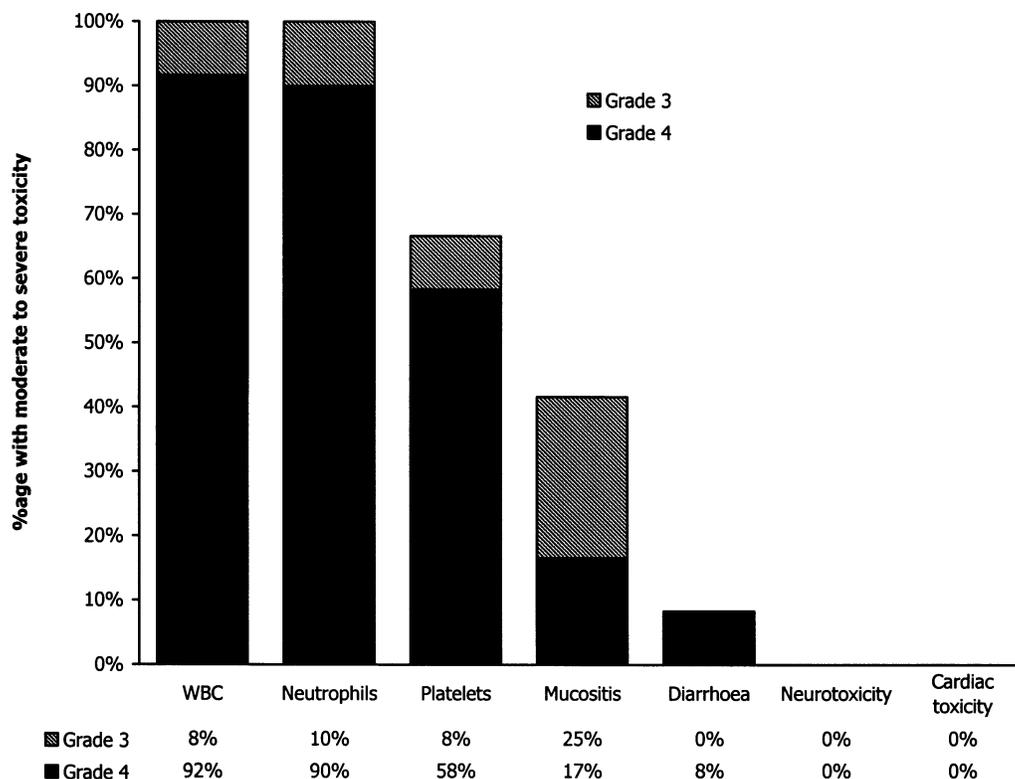


Figure 1. Worst World Health Organization toxicity grade for low-risk patients ($n = 12$) during cyclophosphamide, doxorubicin, vincristine, high-dose methotrexate (CODOX-M). Other toxicities included one grade 3 renal failure and one grade 3 alopecia.

Low risk

The CR rate in LR patients was 83% (10 patients). Of the two remaining patients, one (8%) died from sagittal sinus thrombosis (after cycle 2) that developed as a presumed non-specific complication of intravenous chemotherapy (no further details were available—relatives refused post-mortem) and one (8%) progressed. This patient was initially salvaged with IVAC, hyperfractionated total body irradiation and an allograft. However, he relapsed again 4 months later and died 12 months after initial relapse.

The median follow-up time was 35.9 months (range 10–56 months). No patient achieving CR has relapsed: each was last known to be alive and well, with no relapse events reported, >6 months after starting chemotherapy.

Event-free survival at 1-year was 83.3% (95% CI 61.3% to 99.0%) and at 2-years 83.3% (95% CI 59.0% to 99.0%); OS rate at 1-year was 91.7% (95% CI 75.3% to 99.0%) and at 2-years 81.5% (95% CI 56.1% to 99.0%). Figures 4 and 5 show EFS and OS for LR patients, respectively.

High risk

Twenty-nine (74%) HR patients attained CR after treatment, including four patients who had less than four cycles of alternating CODOX-M/IVAC treatment. Five patients (13%) had

PR, two (5%) NR and three died (7.5%) during chemotherapy: all three reported disease as the primary cause of death, although for two patients infection was implicated and one of these also had Crohn's disease. Five patients (12.5%) who achieved CR have relapsed: four relapsed 3–9 months after starting protocol chemotherapy, the other after 19 months. This late-relapsing patient was last known to be alive 6 months after relapse. One of the four early-relapsing patients was successfully salvaged and was alive and well 3 years later. The other three patients died <6 months after relapse. No patients with NR or PD after chemotherapy were salvaged: none survived >6 months after treatment. However, three patients with PR after chemotherapy achieved CR by their first follow-up visit: two of whom had received no further therapy, whilst the other had an extra CODOX-M cycle. Two of these three patients were last known to be alive 40 and 45 months after finishing protocol chemotherapy, respectively; the other relapsed after 20 months, and was last known to be alive 6 months later.

The median follow-up time is 32 months (range 3–59). Event-free survival at 1 year is 65.0% (95% CI 50.2% to 79.8%) and at 2 years is 59.5% (95% CI 43.0% to 76.0%); OS at 1 year is 70.0% (95% CI 54.4% to 85.5%) and at 2 years is 69.9% (95% CI 52.3% to 87.5%). Figures 4 and 5 display EFS and OS for HR patients.

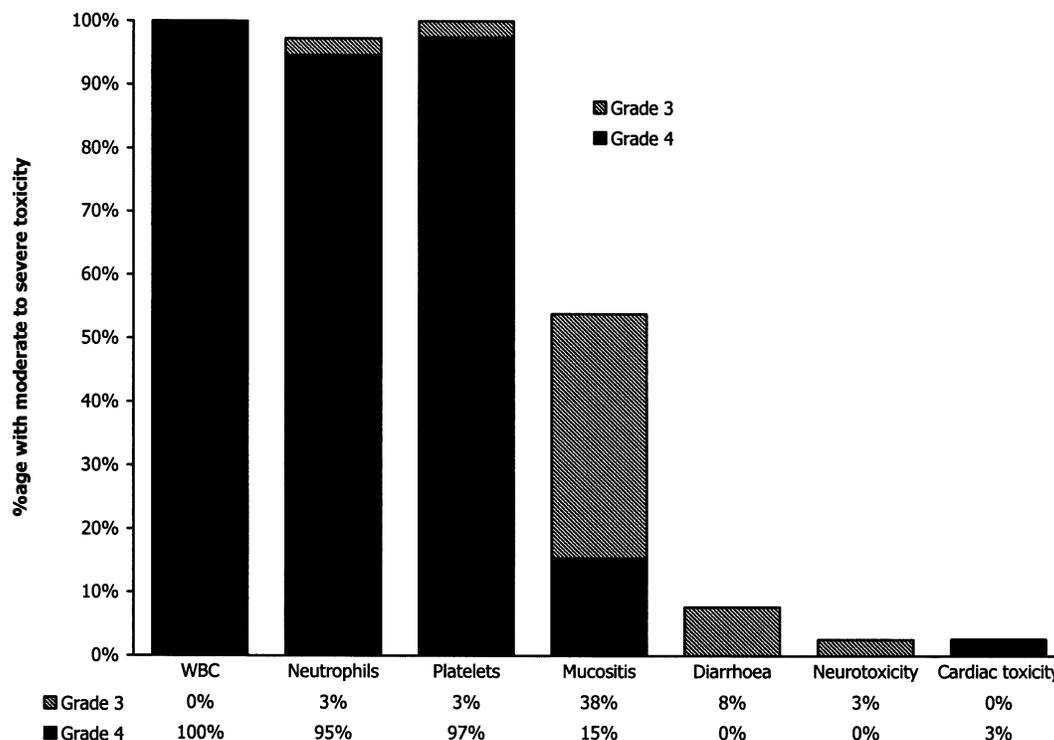


Figure 2. Worst World Health Organization toxicity grade for high-risk patients ($n = 40$) during cyclophosphamide, doxorubicin, vincristine, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide, high-dose cytarabine and intrathecal methotrexate (IVAC). Other toxicities were as follows: grade 3 haemorrhage, one; grade 3 per vaginal bleeding, one; grade 3 lung toxicity, one; grade 3 sepsis, one; grade 4 sepsis, two; grade 4 constipation, one; and grade 3 alopecia, one.

Prognostic factors

The HR group reported here comprises one of the largest groups of consistently treated BL patients in the literature and provides an opportunity to examine prognostic factors, in particular the IPI index, not previously applied to BL patients. This is still, however, a small sample on which to perform these analyses: the findings are considered hypothesis-generating.

Table 4 shows estimates of 1-year EFS for subgroups within this group of 40 patients. A trend was noted towards worsening EFS for older patients, for poorer IPI scores (at least in the short term) and for bone marrow involvement.

Discussion

Burkitt's lymphoma is a rapidly progressive and rare form of NHL, comprising <1% of these cancers according to recent series [4]. Burkitt's lymphoma has been consistently identified by pathologists, using routine stains, in the multiple classifications of lymphoid malignancy that have been derived in the last 20 years [1, 2, 8]. Burkitt's lymphoma is characteristically associated with an 8;14 (or occasionally 2;8 or 8;22) chromosomal translocation that is associated with over-expression of *c-myc*. These changes are thought to be of

great importance in the pathogenesis of this condition, associated as they are with marked increase in mitotic activity such that virtually 100% of cells are in division [27, 28]. The Ki-67 (mib-1) stain used to confirm a diagnosis of BL in this series identifies this mitotic activity and 100% staining of neoplastic cells has been accepted in the recently described WHO classification as a necessary finding in patients with BL [2].

The literature relating to the treatment of adult BL is scant and derived over a long period of time, and therefore, is difficult to interpret because of conflicting views about classification, the probable inclusion of substantial numbers of the less well-defined B-LL and wide variations in patient mix (e.g. median age, incidence of bone marrow involvement). Certainly the 20% rejection of cases in this series by review pathology illustrates the difficulty of diagnosis of this condition by non-expert pathologists. Many regimens have been tested in adult BL, including a Stanford regimen [19], ProMACE-based therapy [23], the French LMB protocols [22, 24], and the German B-NHL [25] regimen. These series cannot easily be compared (for the reasons cited above), but report cure rates in the range 50–70%, often despite bone marrow and CNS involvement [29, 30]. Salvage rates are poor throughout.

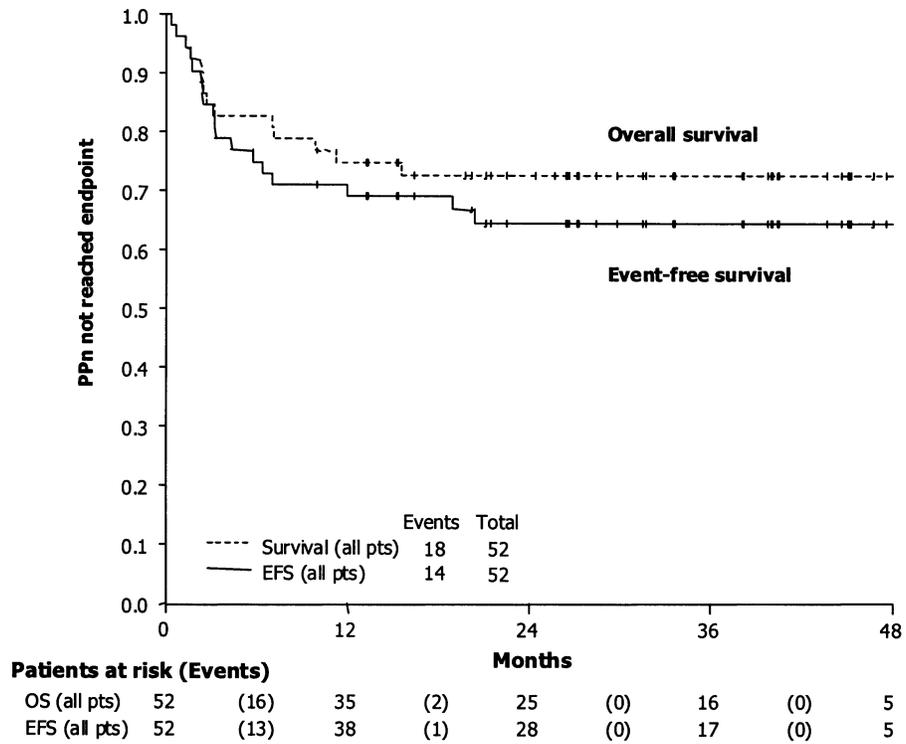


Figure 3. Overall and event-free survival for all patients (pts; n = 52).

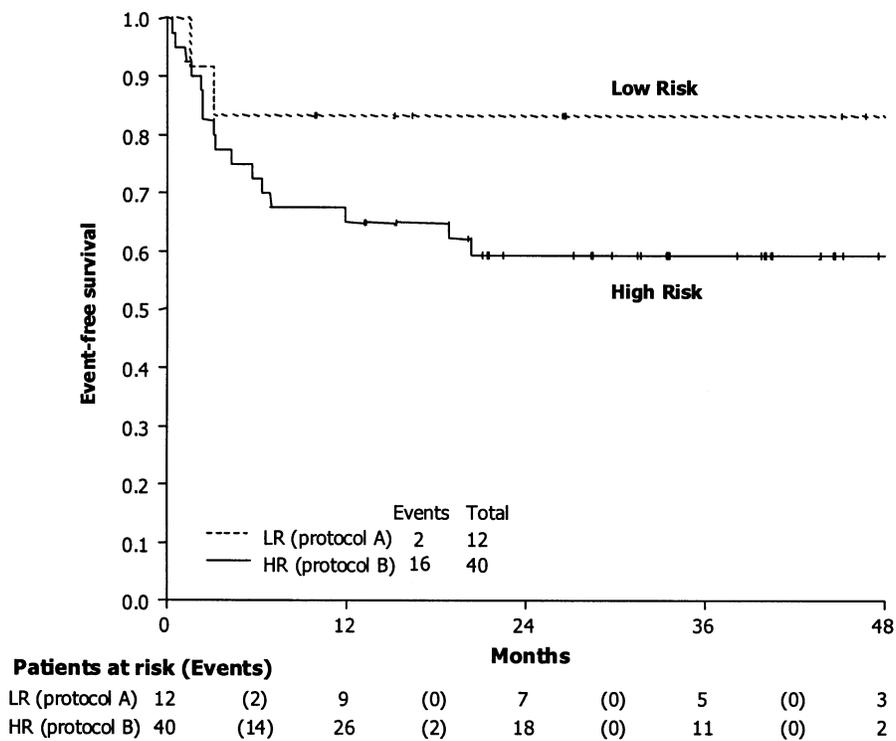


Figure 4. Event-free survival for all patients (n = 52).

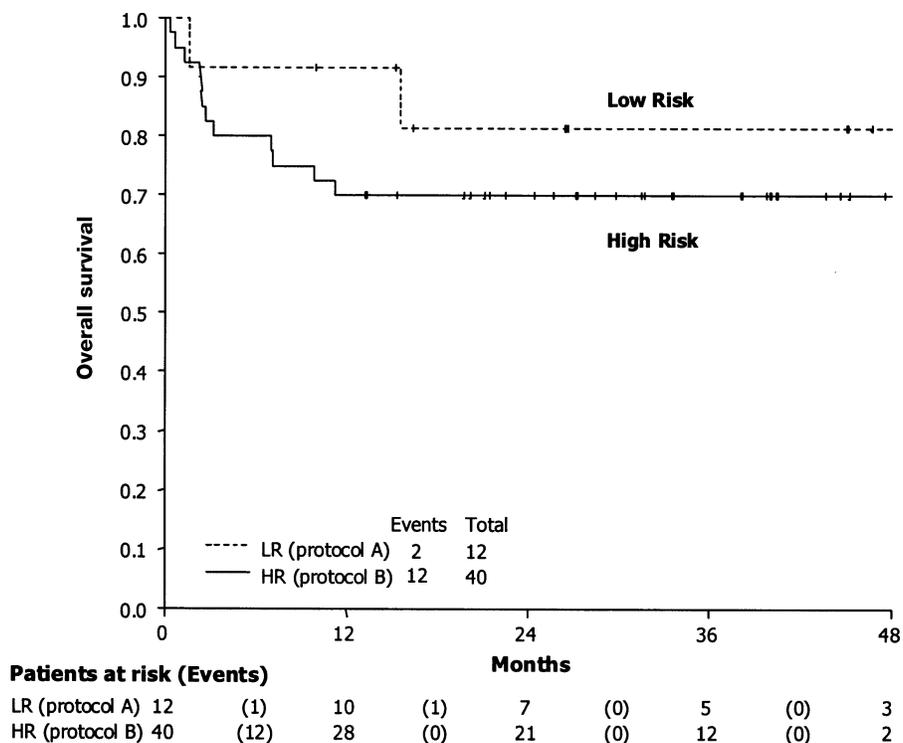


Figure 5. Overall survival for all patients ($n = 52$).

Table 4. Estimate of 1-year event-free survival (EFS) for subgroups of high-risk patients ($n = 40$)

Variable	n	1-year EFS (%) (95% CI)	χ^2	(df)	Log-rank P value
Age (years)					
<30	11	72.7 (46.4–99.0)			
30–49	17	70.6 (48.9–92.2)			
≥ 50	12	50.0 (21.7–78.3)	4.28	(1)	0.1179
Marrow					
Positive	16	43.8 (19.4–68.1)			
Not positive	24	79.2 (62.9–95.4)	3.37	(1)	0.0663 ^a
CNS involvement					
Positive	5	100.0 (47.8–100.0)			
Not positive	35	60.0 (43.5–76.5)	3.06	(1)	0.0802 ^b
International Prognostic Index score ^c					
0–1	6	83.3 (53.5–99.0)			
2	19	63.2 (41.5–84.9)			
3	14	57.1 (31.2–83.1)	0.24	(1)	0.8852

^aHazard ratio (95% CI): 2.64 (0.94–7.43).

^bHazard ratio (95% CI): 0.30 (0.08–1.16).

^cInternational Prognostic Index score missing for one patient.

CI, confidence interval; df, degrees of freedom.

The NCI 89-C-41 [26] regimen on which this study was based evolved from long experience of treating childhood high-grade lymphoma with relatively prolonged CODOX-M chemotherapy. IVAC was designed as a salvage regimen which, when it proved moderately effective, was used as part of initial therapy. In the series reported by Magrath et al. [26], 20 adults (five LR, 15 HR) all remained event-free with 1-year minimum follow-up. Notably, all patients had small non-cleaved lymphoma, but most were of non-Burkitt type (no central pathology review was performed). The median age was 24 years, compared with 35 years in this series; the latter is likely to be more representative of the adult population with this condition.

United Kingdom Lymphoma Group LY06 attempted to confirm the results of Magrath et al. [26] in a multi-group, international setting in a more defined group. The combined 2-year EFS and OS of 65% and 73%, respectively, confirm the high efficacy of this treatment regimen in this condition, with cure possible despite CNS or bone marrow involvement. Chemotherapy salvage after relapse was poor and subsequent survival short, as described previously [31], with no obvious role, currently, for high-dose chemotherapy according to this limited data. Furthermore, it would not be possible to support a previously described role for consolidation high-dose therapy for patients in complete remission [32, 33] as relapse rates were low (0% LR, 10% HR).

This regimen is highly toxic, short-term, particularly manifest by myelosuppression and mucositis. Most patients (particularly with HR disease) required relatively prolonged inpatient care; there was a significant toxic death rate. Almost no long-term toxicity was apparent, with preliminary data suggesting recovery of fertility, at least in females.

Prognostic factor analyses were limited by small patient numbers, but indicated a trend to a worsening EFS with increasing age and marrow involvement. Although the IPI system had not been derived for this patient group the results were not inconsistent with expectations: higher IPI scores being associated with worse EFS.

A follow-on clinico-pathological study has been initiated (CRC LY10) with broadened entry criteria: B-cell lymphoma with 100% Ki-67 staining. An attempt will be made to obtain fresh tissue, at presentation, for cytogenetics. Paraffin blocks will be reviewed centrally with fluorescence *in situ* hybridisation (FISH) studies performed to demonstrate 8;14 and 14;18 translocations, where present. Efforts will be made to make the pathological study all-encompassing by including all protocol-eligible patients, even if untreated, with the recruitment of leukaemic and elderly patients. In an effort to further reduce toxicity, methotrexate doses will be decreased, as will cytarabine in the elderly. This study should better define BL and B-LL clinico-pathologically, and will evaluate the efficacy of CODOX-M/IVAC in high-grade B-cell malignancy of any type.

In summary, BL is a rare neoplasm of young adults which is explosive in onset, often bulky and widespread at presenta-

tion, yet highly curable. This study demonstrated high cure rates with CODOX-M/IVAC in an international patient group which included only non-endemic BL using conventional histological criteria.

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