A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial)

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This prospective study aimed to develop reproducible diagnostic criteria for sporadic Burkitt lymphoma (BL), applicable to routine practice, and to evaluate the efficacy of dose-modified (dm) CODOX-M/IVAC in patients diagnosed using these criteria. The study was open to patients with an aggressive B-cell lymphoma with an MKI67 fraction approaching 100%. Immunophenotype and fluorescent in situ hybridization (FISH) were used to separate BL from other aggressive B-cell lymphomas. BL was characterized by the presence of a *cMYC* rearrangement as a sole cytogenetic abnormality occurring in patients with a germinal center phenotype with absence of BCL-2 expression and abnormal TP53 expression. A total of 128 patients were eligible for the study, of whom 58 were considered to have BL and 70 to have diffuse large B-cell lymphoma (DLBCL). There were 110 clinically fit patients who received dmCODOX-M (methotrexate, dose 3 g/m^2) with or without IVAC according to risk group. The 2-year progression-free survival was 64% (95% confidence interval [CI] 51%-77%) for BL, 55% (95% CI 42%-66%) for DLBCL, 85% (95% CI 73%-97%) for low risk, and 49% (95% CI 38%-60%) for high-risk patients. The observed differences in outcome and other clinical features validate the proposed diagnostic criteria. Compared with the previous trial LY06 with full-dose methotrexate (6.7 g/m^2), there was a reduction in toxicity with comparable outcomes. This study was registered at www.clinicaltrials.gov as NCT00040690. (Blood. 2008;112:2248-2260)

Introduction

Sporadic Burkitt lymphoma (BL) is a rare, non-HIV–related, and highly curable B-cell lymphoma which predominantly occurs in younger adults.[1,2] BL is characterized by the presence of a t(8;14) or variant translocation, resulting in *cMYC* rearrangement and overexpression.[1-3] Cells with deregulated *cMYC* expression have a very high cell-cycle fraction as defined by expression of the nuclear protein MKI67. Cytogenetic analysis of these cases has, until recently, required fresh tissue or leukemic samples, which are rarely available.[4] As a consequence, previously published clinical series were largely based on morphologic interpretation supplemented by immunocytochemical determination of the cell-cycle fraction as suggested in the World Health Organization (WHO) classification.[1,5-10] The classic morphologic features of BL are, however, variable, and affected by fixation, and as a consequence the diagnosis of BL has been subjective and poorly reproducible.[11,12] In addition, 100% MKI67 expression is not specific for cells with *cMYC* rearrangement.

Previous studies have suggested that sporadic BL, defined using these criteria, is usually curable using rapidly cycling, high-intensity chemotherapy regimens with central nervous system (CNS) prophylaxis; CODOX-M/IVAC is one such regime described by Magrath[5] and successfully used in the United Kingdom in modified form in a prospective trial (LY06).[6] CODOX-M/IVAC and similar high-intensity regimens are considered essential for the treatment of BL, but are highly toxic and should be appropriately targeted to those with BL for whom standard therapy would be less effective.

This study was designed to develop reproducible diagnostic criteria for BL which could be applied to routine practice, and to study the clinical features and response to treatment of patients thus identified in comparison with other aggressive B-cell lymphomas. It was recognized that a morphologic diagnosis of BL was unreliable and in order to capture the maximum number of BL patients a more objective screening test was required. Based on the recommendations of the WHO classification[1] a cell-cycle fraction of near 100% (> 95%), defined by immunocytochemical detection of MKI67, was adopted as a primary criteria for trial entry and treatment. The development of FISH techniques applicable to formalin-fixed, paraffin-embedded tissue[13] enabled biopsies from patients in the trial to be characterized further in terms of key translocations with an extended panel of immunocytochemical features.

A principal cause of toxicity in LY06[6] was the use of high-dose methotrexate (6.7 g/m^2) as a component of CODOX-M. The second aim of this study was to improve treatment tolerability while maintaining efficacy by dose-reducing methotrexate to 3 g/m^2.

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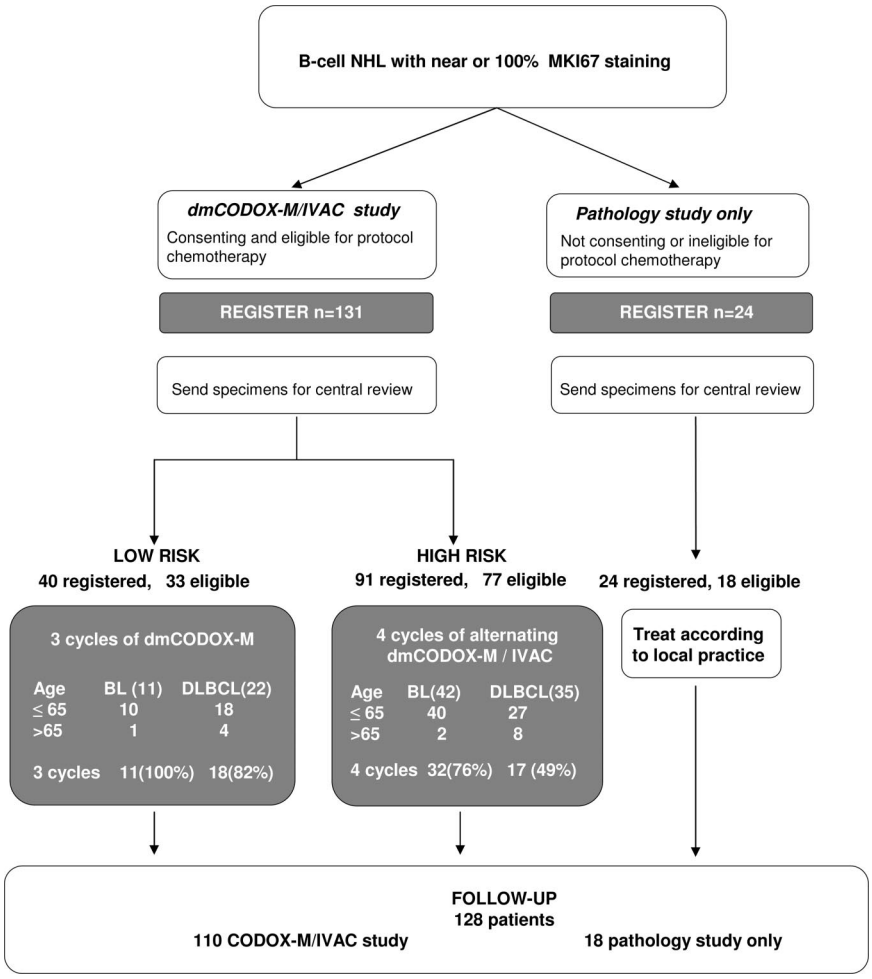

Figure 1. Study profile. Study scheme, patient accrual, risk group, and reference diagnosis.

Methods

Study design

This prospective, international, nonrandomized phase 2 study was initiated and supported by the United Kingdom Medical Research Council Clinical Trials Unit (MRC CTU), London, and the National Cancer Research Institute Lymphoma Clinical Studies Group, and was funded by Cancer Research United Kingdom. It was conducted in collaboration with the Australasian Leukemia and Lymphoma Group (ALLG). The study schema is displayed in Figure 1. Written informed consent was obtained from all patients entered into any aspect of this study. Appropriate central ethical approval was obtained for this trial in the United Kingdom and Australia/New Zealand in accordance with the Declaration of Helsinki.

Eligibility

All patients meeting the following criteria were eligible for inclusion in the pathologic study. Solid tumors: B-cell lymphoma at any site expressing CD20 and/or CD79, and associated with 100% or near (> 95%) MKI67 expression defined using the antibody MIB1; leukemic presentation: evidence of a peripheral B-cell phenotype defined by flow cytometry with absence of CD34 and Tdt. At the time the study opened, MKI67 could not be demonstrated reliably by flow cytometry.

Additionally, to be eligible for the dose-modified (dm) CODOX-M/IVAC study, patients were required to be at least 16 years old, HIV negative, and sufficiently mentally and physically fit to tolerate the treatment regimens. Separate, reduced-dose protocols were recommended for patients older than 65 to increase treatment tolerability.

This protocol was written to allow a single course of COP- or CHOP-like chemotherapy to be given prior to dmCODOX-M induction in patients considered unfit (eg, because of lymphoma-related renal failure) or in whom an initial diagnosis of BL had not been established. It was recommended that protocol dmCODOX-M chemotherapy commence as soon as possible after this treatment, generally between days 14 and 21, or earlier if low-dose chemotherapy was given. Otherwise no previous chemotherapy, or irradiation, or previous malignant disease were allowed in the study.

Trial entry

Patients were registered by contacting the MRC CTU or ALLG (patients from Australia/New Zealand only). Data collection, management, and analyses were performed at the MRC CTU. Patients had to be registered prior to starting protocol therapy or exceptionally (eg, due to public holidays) up to 7 days after starting study treatment.

Pretreatment investigations

Following study entry, patients were evaluated urgently by physical examination with assessment of WHO performance status. Blood was obtained for complete blood cell count (cbc), biochemical profile, lactate dehydrogenase (LDH) urate levels, and HIV serology. A chest x-ray and computed tomography of the chest, abdomen, and pelvis were obtained. Bone scanning and magnetic resonance imaging of the head and axial skeleton was performed as indicated. All patients had a bone marrow trephine and aspirate with cytogenetics where relevant. Cerebrospinal fluid (CSF) was sent for cytology.

Table 1. Dose-modified CODOX-M regimen, with further modification for age older than 65

Day	Drug	Dose	Method	Time
1	Cyclophosphamide	800 mg/m^2	IV	
	Vincristine	1.5 mg/m^2 (max 2 mg)	IV	
	Doxorubicin	40 mg/m^2	IV	
	Cytarabine	70 mg	IT	
2 to 5	Cyclophosphamide	200 mg/m^2	IV	Daily
3	Cytarabine	70 mg	IT	
8	Vincristine	1.5 mg/m^2	IV	
10	Age 65 y or younger			
	Methotrexate	300 mg/m^2	IV	1 h
	Methotrexate	2700 mg/m^2	IV	Given over next 23 h
	Age more than 65 y			
	Methotrexate	100 mg/m^2	IV	1 h
	Methotrexate	900 mg/m^2	IV	Given over next 23 h
11	Leucovorin	15 mg/m^2	IV	At h 36 from start of IV methotrexate
		15 mg/m^2	IV	Every 3 h between 36-48 h
		15 mg/m^2	IV	Then every 6 h until methotrexate level is $< 5\times 10^{-8}$ M
13	G-CSF	5 μg/kg (1 ampoule)	SC	Daily until granulocyte count $> 1\times 10^9$/L then discontinue
15	Methotrexate	12 mg	IT	
16	Leucovorin	15 mg	PO	24 h after IT methotrexate

Next cycle on the day that the unsupported absolute granulocyte count is more than 1.0×10^9/L, with an unsupported platelet count of more than 75×10^9/L.
IV indicates intravenous; IT, intrathecal; SC, subcutaneous; and PO, oral.

Pathology and cytogenetics

Pathology specimens for all patients registered were sent to the Haematological Malignancy Diagnostic Service, Leeds Teaching Hospitals NHS Trust for central review. Detailed immunophenotyping and interphase FISH studies on formalin-fixed, paraffin-embedded tissue sections were carried out. All cases were examined for expression of the following markers: CD20, CD79, C10, CD5, CD23, BCL-2, BCL-6, IRF4, MKI67, FOXP1, TP53, and P21. Biopsies were assessed as + (all or nearly all the tumor cells expressing the marker), − (none or very occasional positive cells) and +/− (a subpopulation of tumor cells expressing the marker). All specimens were studied for the presence of t(8;14)(q24;q32) and alternative *cMYC* rearrangements, t(14;18)(q32;q21) and 3q27 (*BCL-6*) rearrangements using interphase FISH on paraffin sections or isolated nuclei using previously published methods.[13-15]

Treatment

Treatment groups. Patients were considered low risk if they had at least 3 of the following international prognostic index (IPI[16]) factors: normal LDH, WHO performance status 0-1, Ann Arbor stage I to II, and number of extranodal sites less than or equal to 1. These patients were treated with 3 cycles of dose-modified (dm) CODOX-M (the regimen described in our previous study LY06[6] with further adjustment to the methotrexate dose). All remaining cases were regarded as having high-risk disease and received alternating dmCODOX-M/IVAC twice (ie, dmCODOX-M/IVAC/dmCODOX-M/IVAC). Patients older than 65 years were treated with a separately designed protocol incorporating further dose reductions of dmCODOX-M and IVAC.

Protocol treatment schedule. After risk group allocation all patients commenced treatment with dmCODOX-M. This regimen and IVAC are presented in Tables 1 and 2 together with the dose reductions for patients older than 65 years. Prior to chemotherapy all patients commenced oral allopurinol and/or received treatment with rasburicase. Before administration of high-dose methotrexate the measured creatinine clearance had to be greater than 50 mL per minute. Methotrexate was administered over 24 hours regardless of cbc; leucovorin rescue was commenced at 36 hours and continued until the methotrexate level was less than 5×10^{-8} M.

The second cycle was dmCODOX-M for low-risk patients and IVAC for high-risk patients. This, and subsequent cycles, commenced when the absolute granulocyte count without growth factor support was greater than 1.0×10^9/L with an unsupported platelet count of greater than 75×10^9/L. No dose modifications were recommended based on the degree or duration of myelosuppression in previous cycles.

All patients received additional CNS prophylaxis with intrathecal cytarabine and methotrexate (Tables 1 and 2). Patients with proven CNS disease received enhanced CNS-directed therapy either via lumbar puncture or an Ommaya reservoir. This comprised (in addition to intrathecal treatment shown in Tables 1 and 2) intrathecal cytarabine 70 mg on day 5 of dmCODOX-M, and days 7 and 9 of IVAC, and intrathecal methotrexate 12 mg (with leucovorin rescue) on day 17 of dmCODOX-M.

Evaluation. Patients were assessed 3 to 4 weeks after final chemotherapy administration, with relevant repeat radiology and/or a bone marrow. As residual necrotic/fibrotic masses are not unusual in this malignancy, and PET scans were not available in most centers, the primary end point was not response, but progression-free survival, with clinical progression and death from any cause recorded as events.

Statistical considerations

Sample size. In the dmCODOX-M/IVAC study, the primary outcome measure was progression-free survival (PFS). A minimum of 100 eligible patients were required; with an expected 1-year PFS rate of approximately 70% in the group undergoing protocol treatment, this would enable the PFS rate to be estimated with a standard error of less than 5%. The aim of the pathologic study was to register at least 120 patients with clinical and pathologic data. This would enable prognostic factors to be assessed, for example, differences of 25% in the 1-year PFS rate between groups of patients (eg, those with and without t(14;18)) to be detected with approximately 80% power at a 5% significance level.

Analysis methods. Duration of PFS was calculated from the date of the start of chemotherapy to the date of the first appearance of progressive disease or death from any cause; patients known to be alive and without progressive disease at the time of analysis were censored at the time of their last follow-up. Overall survival (OS) was calculated from the date of the start of chemotherapy to the date of death from any cause; patients known to be alive at the time of analysis were censored at the time of their last follow-up. The Kaplan-Meier approach was used to display the PFS and OS estimates in different groups and the curves were compared using the log-rank test. The baseline characteristics between different groups were compared using the χ^2 test for categorical

Table 2. IVAC regimen, with further modification for age older than 65

Day	Drug	Dose	Method	Time
1 to 5	Etoposide	60 mg/m^2 (in 500 mL N saline or 5% dextrose)	IV	Daily over 1 h
	Ifosfamide		IV	Daily over 1 h
	Age 65 y or younger	1.5 g/m^2		
	Age more than 65 y	1 g/m^2		
	Mesna		IV	
	Age 65 y or younger	300 mg/m^2 (mixed with ifosfamide)		Over 1 h
		Then 300 mg/m^2		Every 4 hours × 2
	Age more than 65 y	200 mg/m^2 (mixed with isosfamide)		Over 1 h
		Then 200 mg/m^2		Every 4 hours × 2
1 to 2	Cytarabine		IV	Over 3 h, 12 hourly; total of 4 doses
	Age 65 y or younger	2 g/m^2		
	Age more than 65 y	1 g/m^2		
5	Methotrexate	12 mg	IT	
6	Leucovorin	15 mg	PO	24 h after IT methotrexate
7	G-CSF	5 μg/kg	SC	Daily until granulocyte count > 1.0 × 10^9/L

IVAC starts on day 1 on the first day after CODOX-M that the unsupported absolute granulocyte count is more than 1.0 × 10^9/L, with an unsupported platelet count of more than 75 × 10^9/L. Next cycle (CODOX-M) commences on the day that the unsupported absolute granulocyte count is more than 1.0 × 10^9/L, with an unsupported platelet count of more than 75 × 10^9/L.

data or χ^2 test for trend for ordinal data when appropriate. All P values are 2-sided. An independent Data Monitoring Committee reviewed the trial data approximately annually.

Comparison with LY06. We reanalyzed data from our previous trial (LY06) classifying patients according to the risk groups defined in LY10. We present data stratified by risk group, on patient characteristics, toxicity, and outcome, without formal comparison, in broadly comparable patients in the 2 trials aged younger than 60 years. While the major prognostic factors can be accounted for, it is acknowledged that there may be unknown factors that differ between the 2 study populations and further complicated the comparisons. The results of these comparisons should therefore be viewed cautiously.

Results

Accrual

Between April 2002 and May 2005, 155 patients were registered. These patients were recruited from the United Kingdom (123 patients), Poland (21 patients), Australia (10 patients), and New Zealand (1 patient).

After central pathology review (blind to treatment and outcome), 2 patients were regarded as ineligible. In a further 25 patients no or inadequate pathology material was received for review. Therefore, a total of 128 patients were fully eligible for study, comprising 110 patients treated according to protocol and 18 patients who refused trial entry or were unfit because of comorbid disease to receive protocol treatment.

Pathologic features of the study group

All tumor biopsies were first classified by the central review pathologist, using immunocytochemical criteria. The group was initially subdivided into germinal center (GC) and nongerminal center (nonGC) types using expression of BCL-6, CD10, and IRF4. These groups were further divided into BCL-2–positive and –negative cases and then by abnormal TP53 expression, defined as discordance between TP53 and P21 expression as previously reported.[17-19]

A *cMYC* rearrangement as the sole cytogenetic abnormality by interphase FISH occurred exclusively in tumors with a GC phenotype, absence of BCL-2 expression, and expression of abnormal TP53 (58 tumors, CD20$^+$, CD79$^+$, CD10$^+$, BCL-6$^+$, BCL-2$^-$, P53$^+$, P21$^-$). However, 30% of tumors with this phenotype showed no evidence of *cMYC* rearrangement by FISH. t(14;18) was also found exclusively in the GC group, but BCL-2 was strongly expressed in all these cases. This group included 5 tumors with t(8;14) in combination with t(14;18). A 3q27 rearrangement was found in association with both GC and non-GC phenotypes. In a proportion of tumors with a GC phenotype there was aberrant coexpression of IRF 4 and FOX P1. Neither of these markers is expressed in normal GC B cells.[20-22]

Definition of BL

Based on these findings, BL was defined as a tumor with a germinal center phenotype, absence of BCL-2 expression, abnormal TP53 expression, a *cMYC* rearrangement, and the absence of t(14;18) or 3q27 rearrangements. This definition is used in the analysis of the study presented below. The remainder of the cases entered in the study were considered to be DLBCL, showing considerable heterogeneity in phenotype and cytogenetic characteristics.

Using these criteria, 58 patients were considered to have BL, 53 of whom were entered into the CODOX-M/IVAC study. The remaining 70 patients were diagnosed as having DLBCL, 57 of whom were entered into the CODOX-M/IVAC study. Five (4 CODOX-M/IVAC study, 1 pathology study) of these 70 patients with DLBCL proved to have dual t(8;14) and t(14;18) translocations.

Clinical features of the study group

The features of the patients with BL and DLBCL were clinically distinct and are described in Table 3. Comparison of these patient groups revealed a highly significant difference in median age (BL: 37 years, range 17-76 years; DLBCL: 56 years, range 19-83 years; $P \leq .001$). In addition, the presence/absence of marrow involvement was significantly different (BL 44% vs DLBCL 24%; $P = .016$) as was the presence of B symptoms (BL present 63%, DLBCL 43%; $P = .028$). Risk group allocation also differed (BL low risk to high risk 24%:76%; DLBCL 39%:61%; $P = .057$).

Treatment and outcome

All patients entered into the dmCODOX-M/IVAC study, regardless of review pathology, were treated with dmCODOX-M or dmCO-

Table 3. Clinical features of BL and DLBCL in dmCODOX-M/IVAC and pathology studies

		BL		DLBCL		Total	
		n	%	n	%	n	%
Age, y							
CODOX-M/IVAC*	60 or less	48	91	38	67	86	78
	61 to 65	2	4	7	12	9	8
	More than 65	2	4	12	21	15	14
	Total	53	100	57	100	110	100
	Median (range)	37	(17-76)	55	(19-78)	42	(17-78)
Both*	60 or less	52	90	41	59	93	73
	61 to 65	2	3	10	14	12	9
	More than 65	4	7	19	27	23	18
	Total	58	100	70	100	128	100
	Median (range)	37	(17-76)	56	(19-83)	43	(17-83)
Sex							
CODOX-M/IVAC	Male	42	79	42	74	84	76
	Female	11	21	15	26	26	24
	Total	53	100	57	100	110	100
Both	Male	46	79	46	66	92	72
	Female	12	21	24	34	36	28
	Total	58	100	70	100	128	100
LDH level							
CODOX-M/IVAC	Normal	9	17	18	32	27	25
	Raised	44	83	39	68	83	75
	Total	53	100	57	100	110	100
Both	Normal	12	21	21	30	33	26
	Raised	46	79	49	70	95	74
	Total	58	100	70	100	128	100
WHO PS							
CODOX-M/IVAC	0	18	34	15	26	33	30
	1	15	28	16	28	31	28
	2	8	15	15	26	23	21
	3	10	19	10	18	20	18
	4	2	4	1	2	3	3
	Total	53	100	57	100	110	100
Both	0	20	34	18	26	38	30
	1	17	29	19	27	36	28
	2	9	16	18	26	27	21
	3	10	17	13	19	23	18
	4	2	3	2	3	4	3
	Total	58	100	70	100	128	100
Ann Arbor stage							
CODOC-M/IVAC	I	7	13	12	21	19	17
	II	6	11	12	21	18	16
	III	4	8	5	9	9	8
	IV	36	68	28	49	64	58
	Total	53	100	57	100	110	100
Both	I	10	17	14	20	24	19
	II	6	10	16	23	22	17
	III	5	9	7	10	12	9
	IV	37	64	33	47	70	55
	Total	58	100	70	100	128	100
No. of extranodal sites of disease							
CODOX-M/IVAC	1 or less	26	49	34	60	60	55
	More than 1	27	51	23	40	50	45
	Total	53	100	57	100	110	100
Both	1 or less	29	50	43	61	72	56
	More than 1	29	50	27	39	56	44
	Total	58	100	70	100	128	100

*CODOX-M/IVAC indicates those patients entered into dmCODOX-M/IVAC study only; Both indicates the total patients included in dmCODOX-M/IVAC or pathology study.

DOX-M/IVAC according to risk group. Thirty-seven patients (4 low risk, 33 high risk) were initially treated with 1 course of CHOP (17 patients) or a CHOP-like regimen (20 patients) because of initial diagnostic uncertainty or poor physical condition.

Distribution of patients by diagnostic group, risk group, and age is shown in Figure 1. Fifty-three patients with BL (11 low risk, 42 high risk) and 57 patients with DLBCL (22 low risk, 35 high risk) were entered into the dmCODOX-M/IVAC study.

Table 3. Clinical features of BL and DLBCL in dmCODOX-M/IVAC and pathology studies (continued)

		BL		DLBCL		Total	
		n	%	n	%	n	%
Modified IPI score							
CODOX-M/IVAC*	0	7	13	15	26	22	20
	1	6	11	8	14	14	13
	2	22	42	12	21	34	31
	3	18	34	22	39	40	36
	Total	53	100	57	100	110	100
Both*	0	10	17	17	24	27	21
	1	6	10	11	16	17	13
	2	23	40	15	21	38	30
	3	19	33	27	39	46	36
	Total	58	100	70	100	128	100
Risk group							
CODOX-M/IVAC	Low risk	11	21	22	39	33	30
	High risk	42	79	35	61	77	70
	Total	53	100	57	100	110	100
Both	Low risk	14	24	27	39	41	32
	High risk	44	76	43	61	87	68
	Total	58	100	70	100	128	100
CNS							
CODOX-M/IVAC	Not involved	47	89	48	87	95	88
	Involved	6	11	7	13	13	12
	Unknown	0		2		2	
	Total	53	100	57		110	
Both	Not involved	50	88	60	90	110	89
	Involved	7	12	7	10	14	11
	Unknown	1		3		4	
	Total	58		70		128	
Marrow							
CODOX-M/IVAC	Not involved	29	55	40	71	69	63
	Involved	24	46	16	29	40	37
	Unknown	0		1		1	
	Total	53	100	57		110	
Both	Not involved	32	56	52	76	84	67
	Involved	25	44	16	24	41	33
	Unknown	1		2		3	
	Total	58		70		128	
GI involved (ileocaecal, stomach)							
CODOX-M/IVAC	Not Involved	35	67	44	79	79	73
	Involved	17	33	12	21	29	27
	Unknown	1		1		2	
	Total	53		57		110	
Both	Not involved	39	70	54	79	93	75
	Involved	17	30	14	21	31	25
	Unknown	2		2		4	
	Total	58		70		128	
B symptoms							
CODOX-M/IVAC	No	18	35	35	63	53	49
	Yes	34	65	21	38	55	51
	Unknown	1		1		2	
	Total	53		57		110	
Both	No	21	38	39	57	60	48
	Yes	35	63	29	43	64	52
	Unknown	2		2		4	
	Total	58		70		128	

*CODOX-M/IVAC indicates those patients entered into dmCODOX-M/IVAC study only; Both indicates the total patients included in dmCODOX-M/IVAC or pathology study.

Low-risk protocol

Thirty-three patients (11 BL, 22 DLBCL) commenced this protocol, comprising 3 cycles of dmCODOX-M; 28 were aged 65 or younger and 5 were older than 65 years. Twenty-nine (88%) completed 3 cycles of chemotherapy with 19 of these receiving full-dose protocol treatment. All 11 patients with BL and 18 of 22 patients with DLBCL received 3 cycles of chemotherapy while 3 of 5 patients older than 65 years completed 3 cycles of chemotherapy. In total 4 patients stopped treatment early; one 78-year-old patient died from a CVA 15 days from start of cycle 1

Table 3. Clinical features of BL and DLBCL in dmCODOX-M/IVAC and pathology studies (continued)

		BL		DLBCL		Total	
		n	%	n	%	n	%
Preinduction chemo given							
CODOX-M/IVAC*	No	35	66	38	67	73	66
	CHOP	7	13	10	18	17	15
	COP	0	0	1	2	1	1
	Other	11	21	8	14	19	17
	Total	53	100	57	100	110	100
Both*	No	38	67	50	72	88	70
	CHOP	7	12	10	14	17	13
	COP	0	0	1	1	1	1
	Other	12	21	8	12	20	16
	Unknown	1		1		2	
	Total	58		70		128	

*CODOX-M/IVAC indicates those patients entered into dmCODOX-M/IVAC study only; Both indicates the total patients included in dmCODOX-M/IVAC or pathology study.

(relationship to treatment not determined); and 3 other patients stopped early due to toxicity, change in diagnosis, and time to recover from surgery, respectively.

The median cycle 1-2 interval was 25 days (range 17-86 days), cycle 2-3 was 23 days (range 15-75 days). The comparable figures for our previous LY06 study[5] were cycle 1-2, 22 days (range 18-32 days), cycle 2-3, 22 days (range 16-54 days).

High-risk protocol

Seventy-seven patients commenced this protocol comprising 42 patients with BL and 35 patients with DLBCL; 67 were aged 65 or younger and 10 were older than 65 years. These patients were treated with alternating dmCODOX-M/IVAC. Forty-nine patients (65%) completed 4 courses of treatment with 34 (44%) patients receiving full-dose protocol treatment. Treatment completion differed according to diagnostic group with 32 (76%) of 42 patients with BL and 17 (49%) of 35 patients with DLBCL receiving 4 cycles of chemotherapy. Only 3 of the 10 patients aged over 65 years received 4 cycles of chemotherapy.

In total, treatment was discontinued prematurely in 27 cases, reasons being lack of response or general poor condition (5 patients), progressive disease or disease-related death (12 patients), treatment toxicity (5 patients), treatment-related death (4 patients), and death from other cause (1 died from bronchopneumonia and peritonitis after 3 cycles of treatment). One patient had at least 1 cycle of treatment but further treatment details are missing.

The median cycle 1-2 interval was 27 days (range 17-67 days), cycle 2-3 was 21 days (range 11-37 days), and cycle 3-4, 29 days (range 20-55 days). The comparable figures in the LY06 study[5] were, respectively, 24.5 days (range 16-40 days), 20 days (range 14-41 days), and 27 days (range 18-41 days).

Toxicity

The toxicity assessed using the NCIC Common Toxicity Criteria (CTC Version 2.0) during the chemotherapy is summarized in Table 4. There were 9 deaths (1 low risk, 8 high risk) reported to be treatment-related, of which 5, all high-risk patients, died within

Table 4. Worst toxicity experienced (CTC grade) during the treatment (for 109 patients who received at least 1 cycle of protocol treatment) in dmCODOX-M/IVAC study

	Low risk, N = 33		High risk, N = 76		Total, N = 109	
	n	%	n	%	n	%
WBC						
Grade 3	1	3	0	0	1	1
Grade 4	32	97	75*	99	107	98
Neutropenic fever						
Grade 3	20	61	67	88	87	80
Neutrophil count						
Grade 3	0	0	1	1	1	1
Grade 4	32	97	75	99	107	98
Platelets						
Grade 3	5	15	1	1	6	6
Grade 4	14	42	73	96	87	80
Mucositis						
Grade 3	10	31	29	38	39	36
Grade 4	2	6	8	11	10	9
Unknown	1		0		1	
Neuropath, sensory/motor						
Grade 3	3	10	3	4	6	6
Grade 4	0	0	2	3	2	2
Unknown	3		0		3	

*One patient did not report grade 3/4 leukopenia but received only part of cycle 1 dmCODOX-M prior to disease progression.

12 weeks of starting treatment; 2 of the 9 patients were aged over 65 (66 and 67, respectively).

Progression-free survival and overall survival dmCODOX-M/IVAC study

At the time of analysis, the median follow-up was 29 months (range 3-54 months) with only 2 surviving patients being followed less than 1 year. Forty patients died. The cause of death was disease-related in 29 and treatment-related in 9, with 1 other cause (bronchopneumonia, peritonitis) and 1 death in a 78-year-old patient from a CVA 15 days from start of cycle 1 (relationship to treatment not determined).

Sixty-five patients are alive without progression and 5 alive with progression; 13 patients died without reported progression and 27 patients died after disease progression. Of the 32 patients with disease progression, 20 of whom had further treatment, the median survival time from date of progression was 2 months.

Progression-free survival (PFS) and overall survival (OS) according to risk group are summarized in Table 5. The 2-year PFS was 85% (95% CI 73%-97%) for low-risk patients and 49% (95% CI 38%-60%) for high-risk patients. The 2-year OS was 88% (95% CI 77%-99%) for low-risk patients and 52% (95% CI 41%-63%) for high-risk patients.

Pathologic study

A total of 128 patients were in the pathologic study. At the time of analysis, the median follow-up was 27 months with 46 patients dead and 52 patients with disease progression or death. The PFS and OS by risk group and other prognostic factors were similar to those seen in the subset of 110 patients in the dmCODOX-M/IVAC study (data not shown) and hence subsequent analyses focused on the uniformly treated patients in the dmCODOX-M/IVAC study only.

Comparisons between BL and DLBCL

Overall survival of the BL and DLBCL groups was similar (Figure 2A, Table 5). However, these groups were clinically distinct as previously described, particularly with respect to risk group distribution. Figure 2B shows PFS and OS for patients divided according to risk group and pathology group. In the larger, high-risk group, patients with BL had significantly better PFS (HR = 0.79, $P = .03$) and OS (HR = 0.80, $P = .05$) than patients with DLBCL.

Age

Older patients (> 65 years old who were treated in a separate protocol) clearly have inferior PFS and OS when viewed across all histologies (Table 5). However, within the younger patients (≤ 65), there was no clear age-related trend. Figure 2C shows PFS and OS for patients divided according to age group.

t(14;18), t(8;14), and 3q27 rearrangement

Patients with t(14;18), all in the DLBCL group, have inferior PFS and OS to those with no evidence of t(14;18) (Table 5, Figure 2D). Patients with presence of t(8;14), t(14;18), or 3q27 rearrangement in the DLBCL group also have inferior PFS and OS (Table 5). Four patients were found to have a dual t(8;14) and t(14;18) translocation and this clearly resulted in a marked worsening of prognosis both with regard to PFS and OS. All 4 patients were dead less than 5 months from the start of treatment.

Table 5. Summary of progression-free survival and overall survival in dmCODOX-M/IVAC study

	No. progression or death/total	2-year PFS (95% CI)	Hazard ratio (95% CI), *P*	No. death/total	2-year OS (95% CI)	Hazard ratio (95% CI), *P*
All patients	45/110	60% (51%-69%)		40/110	63% (54%-72%)	
Low risk versus high risk			0.39 (0.21-0.72), .003			0.33 (0.17-0.63), <.001
Low risk	6/33	85% (73%-97%)		4/33	88% (77%-99%)	
High risk	39/77	49% (38%-60%)		36/77	52% (41%-63%)	
BL versus DLBCL			0.77 (0.43-1.38), .38			0.76 (0.41-1.40), .38
BL	19/53	64% (51%-77%)		17/53	67% (54%-80%)	
DLBCL	26/57	55% (42%-68%)		23/57	59% (46%-72%)	
Age 65 y or younger versus age older than 65 y			0.13 (0.05-0.36), <.001			0.11 (0.04-0.32), <.001
65 y or less	33/95	65% (55%-75%)		29/95	69% (60%-78%)	
Older than 65 y	12/15	25% (2%-48%)		11/15	25% (2%-48%)	
Presence of t(14,18)			0.18 (0.055-0.57), .004			0.19 (0.055-0.64), .008
No evidence	33/93	65% (55%-75%)		29/93	73% (64%-82%)	
Present	8/10	20% (0%-45%)		7/10	40% (10%-70%)	
Unknown	7			11		
BL versus DLBCL*			0.33 (0.13-0.82), .017			0.38 (0.14-1.01), .052
BL	19/53	64% (51%-77%)		17/53	67% (54%-80%)	
DLBCL*	11/15	27% (5%-49%)		9/15	40% (15%-65%)	

*Indicates DLBCL with t(8;14)+, t(14;18)+, or 3q27 rearrangement.

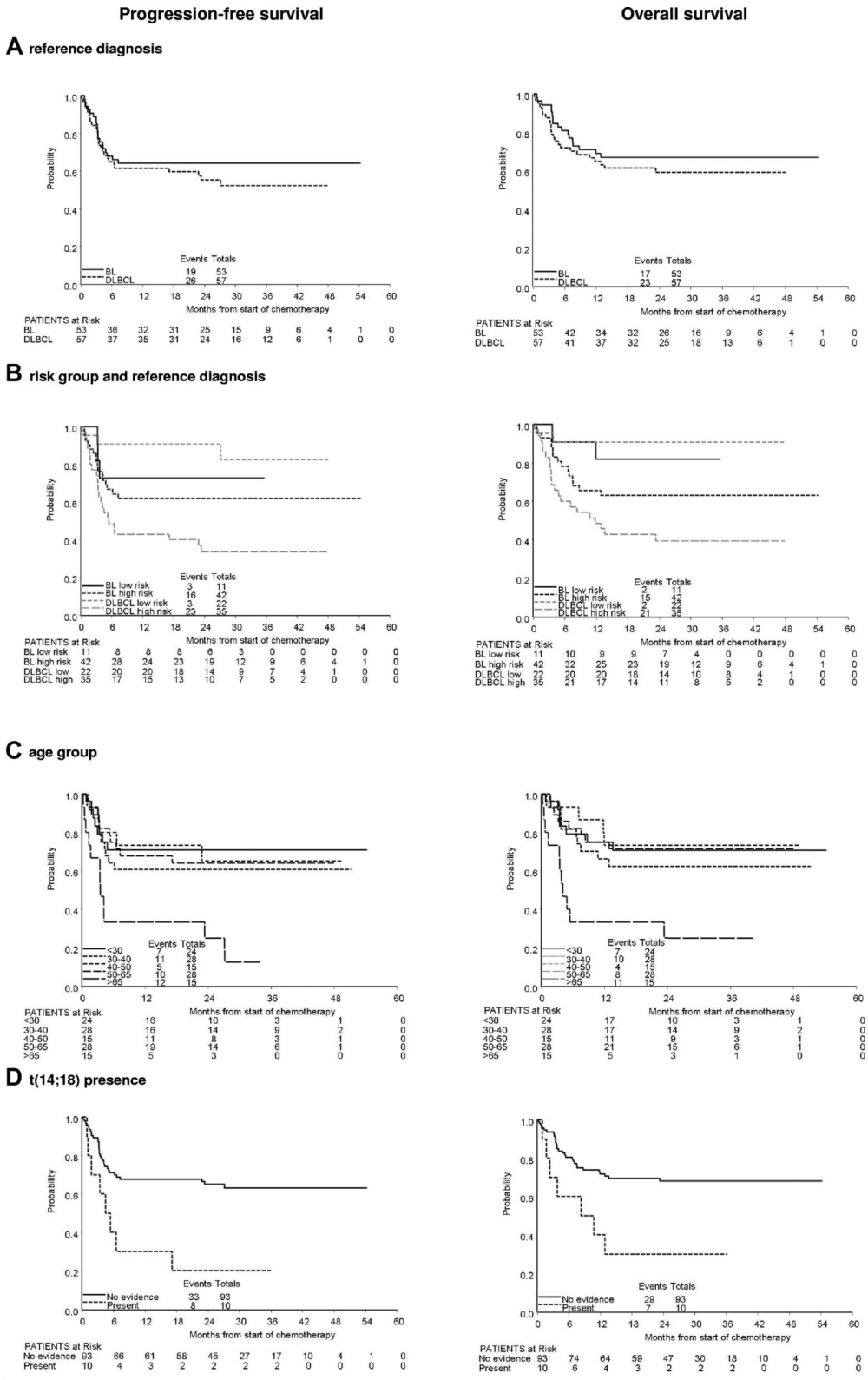

Figure 2. Kaplan-Meier plots of progression-free survival and overall survival. By reference diagnosis (A), risk group and reference diagnosis (B), age group (C), and t(14;18) presence (D).

Prognostic factors

Further exploratory analyses on reference diagnosis, the clinical factors listed in Table 3, and the presence of t(14;18) were performed in the consistently treated high-risk patients (n = 77). There was some evidence of poorer prognosis associated with reference diagnosis of DLBCL (HR = 0.79, $P = .03$), increasing age (continuous variable, HR = 1.03, $P = .02$), CNS involvement

Table 6. Clinical features for patients in LY10 and LY06 (risk group defined as in LY10)

	LY10 CODOX-M/IVAC study patients, risk group defined as in LY10				LY06 patients, risk group defined as in LY10			
	Low risk, N = 24		High risk, N = 62		Low risk, N = 24		High risk, N = 39	
	n	%	n	%	n	%	n	%
Risk group defined as in LY06								
Low risk	NA		NA		15	63	0	0
High risk	NA		NA		9	38	39	100
Median age, y (range)	38	(20-56)	39	(17-60)	32	(15-59)	43	(17-60)
Sex								
Male	20	83	47	76	17	71	22	56
Female	4	17	15	24	7	29	17	44
Ann Arbor stage								
I	16	67	0	0	13	54	0	0
II	8	33	4	6	9	38	3	8
III	0	0	7	11	2	8	6	15
IV	0	0	51	82	0	0	30	77
WHO PS								
0	14	58	12	19	21	88	6	15
1	10	42	17	27	3	13	11	28
2	0	0	17	27	0	0	14	36
3	0	0	14	23	0	0	6	15
4	0	0	2	3	0	0	2	5
LDH level								
Normal	17	71	1	2	22	92	2	5
Raised	7	29	61	98	2	8	37	95
IPI								
0	17	71	0	0	20	83	0	0
1	7	28	2	3	4	17	0	0
2	0	0	30	48	0	0	22	56
3	0	0	30	48	0	0	17	44

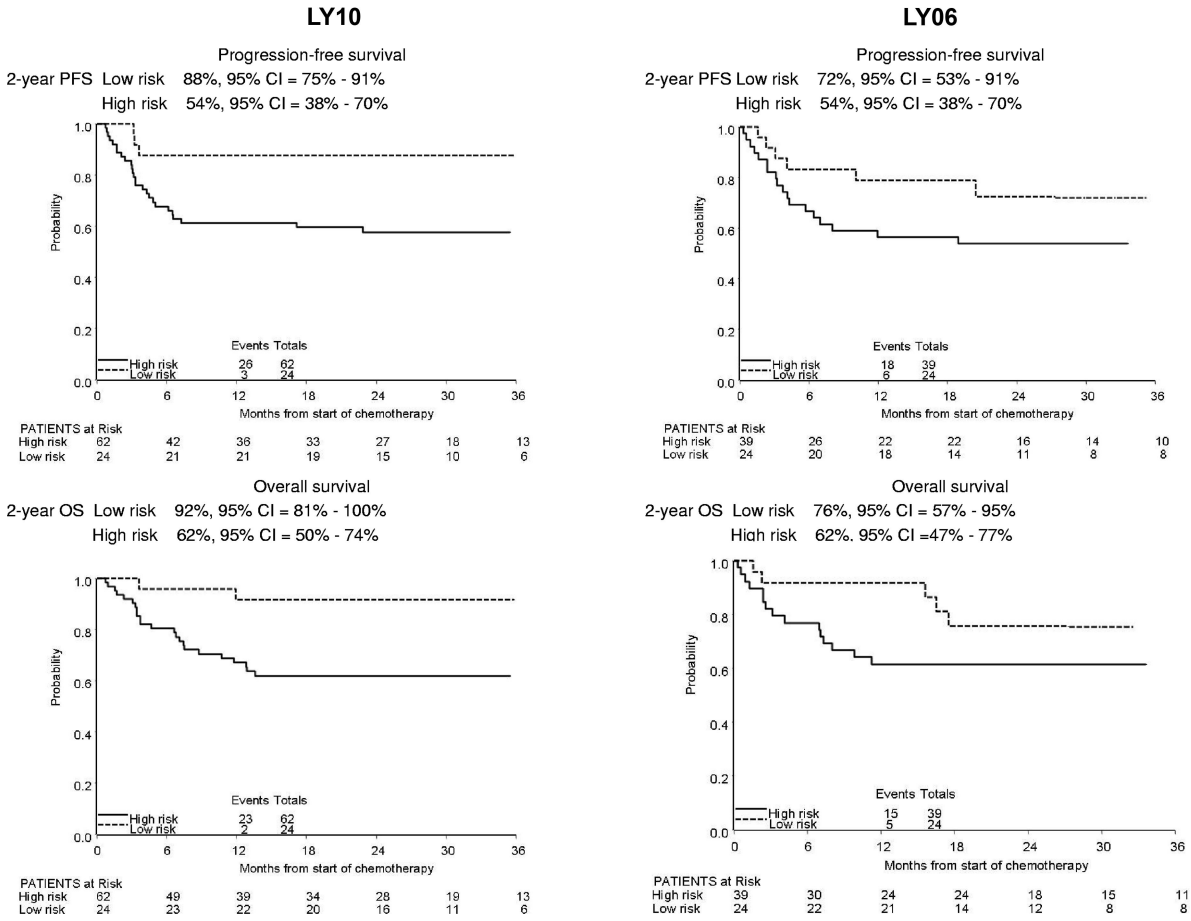

Figure 3. Kaplan-Meier plots of progression-free survival and overall survival in LY10 and LY06 patients with risk group defined as in LY10.

(HR = 2.0, $P = .07$), and t(14;18) presence (HR = 2.7, $P = .02$) on univariate analysis.

LY10 versus LY06

The entry criteria for our previous BL study, LY06,[6] were based on morphologic assessment and MKI67 immunocytochemistry. All patients were younger than 60 years old. FISH was not available at the time of this study, and the pathologic material was not available for further review. BL was therefore diagnosed using the cytologic appearances of the tumor and standard immunophenotyping available at that time. The 2 trial BL populations are therefore not directly comparable, and to minimize bias in the comparison with LY10 with respect to toxicity and outcome, all patients diagnosed with BL or DLBCL and with adequate data on the LY10 risk factors were included (in LY06, 51 were reported to have BL, and 12 were considered to have DLBCL).

Risk group definitions differed between LY10 and LY06, therefore the 63 LY06 patients were reanalyzed according to the LY10 risk group definitions, resulting in 9 LY06 high-risk patients moving to the LY10 low-risk group. The clinical features of patients younger than 60 years in the 2 trials are summarized by risk group in Table 6 and were comparable. PFS and OS curves were remarkably similar (Figure 3). In LY06 the 2-year PFS in the low-risk group was 72% (95% CI 53%-91%) and in the high-risk group 54% (95% CI 38%-70%). The comparable figures in LY10 were 88% (95% CI 75%-91%) and 54% (95% CI 38%-70%). In LY06 the 2-year OS in the low-risk group was 76% (95% CI 57%-95%) and in the high-risk group 62% (95% CI 47%-77%). In LY10 the 2-year OS in the low-risk group was 92% (95% CI 81%-100%), and in the high-risk group 62% (95% CI 50%-74%).

Nadir WBC and neutrophil counts were similar between the 2 trials; however, mucositis was slightly reduced in LY10; the incidence of grade 3/4 mucositis in low-risk patients in LY10 and LY06 were, respectively, 39%/0% and 26%/22% with corresponding figures for high-risk patients of 35%/8% in LY10 and 34%/18% in LY06.

Discussion

BL is a rare form of non-Hodgkin lymphoma comprising no more than 1% of cases. There are no randomized trials in this condition. Previous published series have comprised modest-sized single institution or multigroup evaluations of complex cycling chemotherapy using diverse entry criteria.[5-10] Most commonly in older studies this has comprised typical tumor morphology on hematoxylin and eosin (H&E) histology; more recently 100% MKI67 staining has been used as a surrogate for the diagnosis of BL, occasionally supported by cytogenetics demonstrating a *cMYC* rearrangment.[4] This study is the first to treat all patients consistently with a highly active BL regime using robust diagnostic criteria based on immunophenotyping and interphase FISH.

The use of high MKI67 expression as the primary entry criterion in this study was designed to increase the consistency of recruitment of patients and reduce dependence on unreliable and subjective morphologic criteria. However, the patient population recruited using these criteria proved to be highly heterogeneous

with respect to immunophenotypic and cytogenetic features. Based on these findings high MKI67 alone should not be used as a screening test for BL.

All of the tumors in this study with a *cMYC* rearrangement had a GC phenotype with expression of CD10 and BCL-6, suggesting that somatic hypermutation and class switch recombination may be important in the generation of the translocation. In most cases this appeared to be a highly aberrant germinal center phenotype with coexpression of BCL-6, IRF-4, and FOXP1 not seen in normal germinal center B cells. In experimental systems, inactivation of P53 is essential for *cMYC*-mediated oncogenesis[23-25] and in this study the *cMYC* rearranged tumors all showed evidence of mutated *P53* with strong nuclear staining for the P53 protein in the absence of P21. In tumors with this set of features and absence of BCL-2 expression there was no evidence of a t(14;18), 3q27 rearrangement or significant aneuploidy by FISH. For the purpose of this study this was adopted as the definition of BL. This group showed distinctive clinical and demographic differences from the other patients in the trial. There were, however, no significant differences in multiple other parameters including disease sites at presentation, incidence of CNS disease, stage, IPI score, or other clinical features. Although highly uniform in many respects only a minority of these cases showed classic Burkitt-type morphology. At a practical level, the immunophenotype described above identifies BL with a sensitivity of 100% and specificity of around 70%. When these features are present FISH studies should always be carried out. It is possible that the specificity may be further improved by the addition of further markers such as TCL1.[26]

This approach to the diagnosis of Burkitt lymphoma has been supported by the publication of 2 gene expression studies[27,28] that identified a unique BL gene expression signature distinct from other types of aggressive B-cell lymphoma. Hummel et al[27] emphasized the distinctive characteristics of the molecular BL group in which a *cMYC* rearrangement was the sole abnormality. Gene expression analysis is, however, not a routine diagnostic technique, and the rapid deterioration of many BL samples due to apoptosis is a significant obstacle. However, it is likely that the group defined in our studies using immunocytochemistry and FISH is the same as the molecular BL categories defined in these studies.

The definition of BL needs to be justified by reference to clinical data and in particular the utility of this approach in targeting high-intensity chemotherapy. In this study dmCODOX-M/IVAC proved to be a highly effective treatment in the BL group with an overall survival of 67%, and an excellent outcome in the low-risk group defined by IPI. The effectiveness of the IPI in predicting outcome was much less for the BL group than for DLBCL and in high-risk patients there was a greatly reduced risk of disease progression after chemotherapy in the BL group compared with the DLBCL group. Of the 110 dmCODOX-M/IVAC study patients, the deaths of 9 (8%) were attributed to treatment toxicity, emphasizing the need to target this therapy to those with disease not adequately treated by CHOP-R. Although historic comparison needs to be treated with caution, particularly in view of the diagnostic problems in previous trials, it does not appear that the reduction in methotrexate dose was associated with a less favorable outcome. This should improve the tolerability of the regimen for a broader group of patients.

The majority of patients with a high MKI67 did not meet the definition of BL used in this study and so can act as a comparison group in which to assess the efficacy of this treatment in patients with DLBCL. The overall survival in this group was not significantly different from the BL group as a whole. However, the outcome of this group was also broadly similar to that achieved in most recent trials of CHOP-R–containing regimens, which are much less toxic.[29-32] In contrast to BL, there is a continuing rate of relapse in this group, as would be expected in any series of DLBCL. An important question is the efficacy of CODOX-M/IVAC in patients with DLBCL who have poor prognostic factors. In this study the difference in outcome between IPI groups persisted, those with high IPI having a significantly worse outcome. In the absence of randomized data it is not possible to comment on whether the high IPI patients had a better survival than would be expected with CHOP-type therapy or whether the addition of rituximab to CODOX-M/IVAC would improve the outcome of this poor prognosis group.

One group that is known to have a very poor outcome are patients who have tumors that have multiple chromosomal abnormalities[4,33,34] with combinations of *cMYC, BCL-6,* and *BCL-2* rearrangements. In this study, high-intensity chemotherapy does not appear to have been effective in overcoming the adverse effect of the translocation. A poorer outcome was also found in patients without *cMYC* rearrangement but with t(14:18) or 3q27 abnormalities. These data suggest that increasing the intensity of treatment of patients with DLBCL using dmCODOX-M/IVAC does not negate significantly the effects of the adverse prognostic factors that apply to CHOP-treated patients.

This trial incorporated dose reduction of methotrexate, given as part of CODOX-M from 6.7 g/m^2 to 3 g/m^2. There was some evidence that this approach was less toxic. It was also anticipated that this dose reduction may enable chemotherapy to be more rapidly cycled because of lesser degrees of mucositis. However, this did not prove to be the case when the cycling time was compared with our previous study. There is little or no prospect that randomized trials will be performed in this condition now or in the future and it can be reasonably concluded from our and other data[7] that methotrexate given at a dose of 3g/m^2 is of similar efficacy and can be regarded as an acceptable standard.

The trial was designed to include older patients who are poorly represented in previously published studies. A dose-modified protocol was recommended, but relatively few patients were accrued. As previously described, results from this patient group were inferior and the treatment poorly tolerated with few patients treated effectively.

Rituximab is now in widespread use in B-cell lymphoma treatment and has been shown to increase cure rates in DLBCL. This drug was not incorporated into the treatment given in this trial as it was not a standard treatment and not licensed when the study was designed. Rituximab has been described as having possible beneficial effects, particularly in older patients.[10] It seems highly unlikely that randomized trials testing the efficacy of this drug will be performed in the future. Clinicians may decide they wish to add this agent to treatments in this young patient population.

In conclusion we have proposed a set of robust diagnostic criteria for the identification of patients with nonendemic BL that can be used to effectively target high-intensity chemotherapy. These patients have a good outcome when treated with dose-modified CODOX-M/IVAC, and this should now be considered as a standard therapy for BL. In contrast, the trial does not support the routine use of high-intensity therapy in other highly proliferative B-cell lymphomas. There was no clear evidence that this treatment would be efficacious for non–BL patients who would currently conventionally be treated with CHOP-R with more acceptable toxicity.

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Authorship

Contribution: G.M.M., A.J., and S.P.S. designed the study; S.B. and A.J. performed the central pathology review and laboratory analyses and derived the diagnostic criteria for BL; G.M.M., J.W., J.A.R., and M.W. (representing the ALLG) entered more than 10 patients; S.M.C. and C.L.Y. were responsible for the data management; W.Q. and S.P.S. performed statistical analysis; G.M.M., W.Q., S.P.S., and A.J. drafted the manuscript; all authors contributed to and approved the manuscript.

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