bjh research paper

Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002

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Received 27 August 2013; accepted for publication 8 November 2013

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Prior Presentations: Selected as an Oral Presentation for ASH 2010.

Summary

To improve long-term outcomes for Burkitt leukaemia/lymphoma (BL) or aggressive lymphomas in adults, we assessed the benefit of adding rituximab and filgrastim support to a dose-dense modified chemotherapy regimen from the Cancer and Leukemia Group B (CALGB) 9251 trial. One hundred and five patients (aged 19–79 years) were enrolled; 27% were >60 years old; 47% had high or high-intermediate risk by International Prognostic Index (IPI) criteria. Common severe toxicities included stomatitis/upper gastrointestinal toxicity (69%), renal insufficiency (10%), neurological events (25%) and pulmonary events (18%). Seven died from treatment-related causes (one central nervous system bleed, four infections, two respiratory failure); five were >60 years old. Results in this adult population are encouraging as complete response (CR) was observed in 83% and 4-year event-free (EFS) and overall survivals (OS) were 74% and 78%, respectively. Results compare favourably to our prior chemotherapy alone study (CALGB 9251) but despite this, high-risk patients still had worse outcomes. In conclusion, short duration, intensive chemo-immunotherapy is feasible and should be considered in adults with BL as it results in high remission rates and durable remissions.

Keywords: Burkitt leukaemia, Burkitt lymphoma, chemo-immunotherapy, rituximab.

Burkitt leukaemia/lymphoma (BL) is a rapidly progressive B-cell malignancy that often presents in extranodal sites or as an acute leukaemia. Characteristically, the monomorphic medium-sized Burkitt cells bear a translocation of *MYC*, but this is not specific and the gold standard for diagnosis, i.e., the distinction between BL and other aggressive B-cell lymphomas, continues to evolve (Leoncini *et al*, 2008). Typical Burkitt tumour cell immunophenotype entails expression of moderate to strong levels of immunoglobulin (Ig)M with light chain restriction plus CD19, CD20, CD22, CD10, BCL6, and CD38, but rarely BCL2 and never TdT. Greater than 90% of the cells express the proliferation antigen, Ki67. Cytogenetically, most cases of BL have *MYC* translocation from band 8q24 to the *IGH* chain region, 14q32 or, less commonly to the lambda (*IGL*, 22q11) or kappa (*IGK*, 2p12) locus (Simon *et al*, 1988). During the time this study was conducted (2002–11), definitions differed from today's more precise characterization, and cases with features intermediate between Burkitt and diffuse large B-cell lymphoma were often termed 'Burkitt-like' in the older terminology. More recently, this group has been subsumed in the current nomenclature by 'B cell lymphoma unclassifiable with

First published online 15 January 2014
doi: 10.1111/bjh.12736

features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma'. Thus, this report presents the data for all treated patients, but also the subgroup of 58 with central pathology review and confirmation of Burkitt disease using our current definitions (Leoncini *et al*, 2008).

Despite high initial response rates, cures for adults with BL were uncommon when standard diffuse large B-cell or acute lymphoblastic leukaemia regimens were used. When laboratory evidence demonstrated that Burkitt cells had a high proliferative rate and were highly sensitive to alkylating agents and antimetabolites, regimens with fractionated cyclophosphamide, high-dose methotrexate and high-dose cytarabine were developed that improved outcomes (Hoelzer *et al*, 1996; Magrath *et al*, 1996). In the Cancer and Leukemia Group B (CALGB) 9251 study, we evaluated a dose dense, intensive chemotherapy regimen resulting in a high overall survival (OS) rate of 52% (43–60%). However, outcomes were clearly worse for older patients and those classified as high risk by the International Prognostic Index (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project's, 1993; Rizzieri *et al*, 2004). The strong expression of the surface antigen CD20 in BL led to its use in BL with encouraging results in small studies (Thomas *et al*, 2006; Maruyama *et al*, 2010;; Mohamedbhai *et al*, 2011). Additionally, the expected incidence and duration of severe neutropenia observed in CALGB 9251 suggested that primary prophylaxis with myeloid growth factor support might prove beneficial. Thus, CALGB study 10 002 (Alliance) was designed as a phase two study for patients with Burkitt or Burkitt-like leukaemia/lymphoma (Harris *et al*, 1999) to determine the response rate, event-free survival (EFS), and OS of adults receiving rituximab with short duration, high intensity chemotherapy with filgrastim support.

Patients and methods

Eligible patients were those ≥16 years of age, previously untreated with a diagnosis of Burkitt or 'Burkitt-like' leukaemia or lymphoma per the definitions used at the time of study conduct (Diebold *et al*, 2001) and who were not known to be human immunodeficiency virus (HIV) positive. Patients were enrolled based on pathology diagnosis by their local haematopathologist, though confirmatory material was requested for central pathology review. Liver and kidney function <1·5 times the upper limit of normal (ULN) was required, unless the abnormal function was felt, in the investigator's opinion, to be due to the disease. Local institutional review boards at participating institutions approved the study, and all patients provided written informed consent. This study was listed on clinicaltrials.gov as NCT00039130.

Treatment

The treatment regimen is outlined in Table I. Patients could not have received any therapy for their disease prior to enrollment and initiation of therapy on this study. Following a week of cytoreduction (cycle 1), patients received alternating cycles of multiagent therapy with filgrastim every 3 weeks for six more cycles, given over 19 weeks. Delays were allowed until the absolute neutrophil count had recovered to $\geq 1{\cdot}0 \times 10^9$/l, platelet count $\geq 75 \times 10^9$/l, and the patient had been off growth factor for more than 2 days. In addition, the patient must have recovered from therapy-induced mucositis. Known large effusions were expected to be drained prior to the administration of methotrexate and this agent was held in any cycle in which the creatinine clearance was <50 ml/min. Predefined dose reduction algorithms were utilized for hepatic dysfunction (vincristine, etoposide, doxorubicin, cyclophosphamide), central nervous system toxicity (doxorubicin), peripheral nervous system toxicity (vincristine) and cerebellar toxicity (cytarabine). All patients were screened for hepatitis B and those positive were closely monitored for reactivation. Unless there was clinical concern for central nervous system (CNS) involvement, a lumbar puncture (LP) was not performed until the start of cycle 2 (day 8), and then one dose of triple intrathecal therapy was given with each of cycles 2–7. Patients proven to have CNS disease continued to receive systemic therapy with the addition of triple intrathecal therapy twice weekly until the cerebrospinal fluid was clear, then monthly for fore treatments, followed by cranial radiation with 2400 cGy in 12 fractions. Those with gonadal disease received 2600 cGy to the testes during systemic therapy. Rituximab was first administered using stepped-up dosing in cycle 2, then at standard dosing, once per cycle for courses 3–7 (Table I).

Evaluation and response criteria

Toxicity was monitored in all patients using the CALGB-expanded National Cancer Institute Common Toxicity Criteria, version 2.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf) and was monitored throughout therapy as well as during follow-up if late toxicities were noted. Radiographic scans of the chest, abdomen and pelvis as well as other known areas of disease in patients with lymphoma were required after every two courses of therapy, as were bone marrow examinations in patients with marrow involvement. Response criterion followed the standard at the time, which mirrors the updated criterion by Cheson *et al* (2007), however this is less stringent than current criterion for lymphoma response, which requires nodal masses in aggressive lymphomas to have functional evaluation with positron emission tomography (PET) imaging for response to be assessed. While this was commonly done for patients on this study, it was not mandated as early in the study gallium scans were used in some cases instead.

Statistical methods

This phase II study was powered for 100 evaluable patients with the expectation that about 85% of the subjects would

Table I. CALGB 10 002 treatment schema.

Cycle 1	Dose-Schedule based on actual weight	Days given
Cyclophosphamide	200 mg/m^2/d	1–5
Prednisone	60 mg/m^2/d oral	1–7
Allopurinol	300 mg/d oral	1–14
Cycles 2, 4, and 6		**Cycle length 21 d**
Ifosfamide	800 mg/m^2/d over 1 h with Mesna	1–5
Dexamethasone	10 mg/m^2/d	1–5
Methotrexate§	150 mg/m^2 load, then 1·35 g/m^2 over 23·5 h	1
Leucovorin*	25 mg/m^2 36 h after initiation of methotrexate, then 10 mg/m^2 every 6 h until level <0·05 μmol/l	2
Vincristine	2 mg push	1
Cytarabine	1000 mg/m^2/d over 2 h	4–5
Etoposide	80 mg/m^2/d over 1 h	4–5
Filgrastim	5 μg/kg/d	Seven, until ANC > 0·5 × 10^9/l
Rituximab	†	Eight, 10 and 12 of cycle 2 only
Rituximab	†	Eight of cycle 4 and 6
Intrathecal therapy	‡	1
Cycles 3, 5 and 7		**Cycle length 21 d**
Cyclophosphamide	200 mg/m^2/d	1–5
Dexamethasone*	10 mg/m^2/d	1–5
Methotrexate§	150 mg/m^2 load, then 1·35 g/m^2 over 23·5 h	1
Leucovorin†	50 mg/m^2 36 h after initiation of methotrexate, then 10 mg/m^2 every 6 h until level <0·05 μmol/l	2
Vincristine	2 mg push	1
Doxorubicin	25 mg/m^2/d	4–5
Filgrastim	5 μg/kg/d	7, until ANC> 0·5 × 10^9/l
Rituximab	†	8
Intrathecal therapy	‡	1

CALGB, Cancer and Leukemia Group B; ANC, absolute neutrophil count.

*Intravenous or oral.

†Rituximab administered in cycle 2 at a dose of 50 mg/m^2 on day 8 and 375 mg/m^2/d on days 10 and 12. For cycles 3–7, rituximab was given at 375 mg/m^2 only on day 8 of each cycle.

‡Intrathecal therapy Methotrexate 15 mg, Cytarabine 40 mg, Hydrocortisone 50 mg; Patients with central nervous system disease received additional intrathecal therapy twice weekly until clear of malignant cells, then once weekly for 4 weeks, then radiotherapy was initiated.

§Methotrexate dose held for creatinine clearance <50 ml/min.

be under 60 years of age and this stratum was used to test the null hypothesis that the complete response (CR) rate with this treatment is ≤60% in those <60 years old *versus* the alternative hypothesis that the CR rate is ≥80%, with type I and type II error rates of approximately 0·08 and 0·1, respectively. The response rates for those ≥60 years old were calculated and presented descriptively. Formal disease status evaluation was planned for every 3 months in the first 2 years, every 6 months for three more years and annually for five more. Endpoints were censored at the time of last clinical evaluation for disease-free and event-free status. OS was measured from study entry to death from any cause or censored on the date last known alive. Treatment failure was defined as progressive disease, death from any cause, or removal from protocol therapy without response. Survival function estimates were computed using the product-limit method and survival distributions were compared using the log-rank test (Kalbfleisch & Prentice, 1980). The database was updated for this analysis on October 30, 2013.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (Durham, NC, USA). As part of the quality assurance program of the CALGB (ALLIANCE), members of the audit Committee visited all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumour response and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 29 patients of the 105 patients under this study.

Results

Patient characteristics

The study was activated on 15 May 2002 and closed to accrual on 29 September 2009, with 105 patients enrolled. The median follow-up time for the 80 survivors was 6·4 years with a range of 2·4–10·3 years. Using the WHO classification at the time the study was enacted (Diebold *et al*, 2001), 89 had classic Burkitt and 16 had Burkitt-like leukaemia/lymphoma according to the local haematopathologist's diagnosis. Using the definition of >25% marrow involvement or any peripheral blood Burkitt cells to define leukaemia, there were 29 (28%) patients with leukaemia and 76 (72%) with lymphoma. Ninety-seven patients had *MYC* analysed and 79 were positive by either local or central pathology testing. Ten of the lymphoma patients and six of the leukaemia patients had Burkitt-like histology. Material for central pathology review was obtained for 104 (99%) with 99 (94%) having sufficient material to render a diagnosis. Using the definitions employed at the time the protocol was initiated (Diebold *et al*, 2001), 58 patients were confirmed as BL, 20 as probable Burkitt lymphoma; 21 were felt on central review to be a different high risk, aggressive lymphoma such as 'double hit' or ALL. Using current definitions (Leoncini *et al*, 2008), the 58 confirmed as BL remained so, though 16 were felt to likely be Burkitt but with insufficient material for complete central confirmation of pathology, and 25 were other high-risk subtypes.

Table II summarizes the pretreatment characteristics and known risk factors for all patients. Additionally, 14 (14%) presented with CNS disease. There were major differences between the two age cohorts with more males in the younger group (80% vs. 39%; $P < 0{\cdot}0001$) and there was a greater percentage of higher IPI risk patients in the ≥60 cohort ($P < 0{\cdot}0001$).

Treatment delivery and toxicity

Overall, 81 patients (77%) completed at least six of the seven planned cycles of therapy, with the median time between cycles of 3 weeks. Adverse non-fatal events or patient withdrawal accounted for 16 patients (15%) not completing all cycles. There were nine patients who ended treatment due to death. Five were treatment-related and four died of progressive disease (two actively being treated and two who withdrew early and later progressed). Two additional patients died of treatment-related complications after all therapy was completed: one died 2 months after all therapy completed and one withdrew due to toxicities after three cycles and died 2 months later, though neither had progressive disease at the time of death. Thus seven deaths were felt to be directly related to the therapy. Two deaths were in the <60-year-old cohort (one infection and one pulmonary failure) and five in

Table II. Pretreatment characteristics for all 105 patients enrolled on CALGB 10 002 and for comparison 133 patients enrolled on the previous study CALGB 9251. The current study included: 15% Burkitt-like disease, 28% with leukaemia and 14% with central nervous system disease at diagnosis, compared with 22%, 38% and 8%, respectively, in CALGB 9251.

Characteristic	<60 years old (%)	≥60 years old (%)	*P*-value (comparing ages)	CALGB 10 002 Total (%)	CALGB 9251 (Rizzieri *et al*, 2004) (%)	*P*-value (comparing studies)
Patients (*n*)	77	28		105	133	
Median age, years (range)	36 (19–59)	64 (60–79)		43 (19–79)	48 (17–78)	0·411
Age ≥60 years				28 (27)	32 (24)	0·769
Males, *n* (%)	62 (80)	11 (39)	<0·0001	73 (69·5)	92 (69)	0·954
Race			0·92			0·450
White	68 (88)	25 (89)		93 (89)	118 (89)	
Hispanic	4 (5)	1 (4)		5 (5)	3 (1)	
Black	4 (5)	1 (4)		5 (5)	10 (8)	
Asian	1 (1)	1 (1)		2 (2)	2 (1)	
Missing					1 (1)	
B symptoms	38 (49)	12 (43)	0·66	50 (48)	72 (55)	0·289
Performance status (CALGB) ≥2	17 (22)	8 (29)	0·61	25 (24)	40 (30)	0·281
≥2 Extra-nodal sites	46 (60)	13 (46)	0·27	59 (56)	51 (38)	0·006
Elevated LDH	52 (67)	22 (79)	0·34	74 (70)	116 (87)	0·001
Lymphoma Stage 3 or 4	35 (45)	16 (57)	0·38	51 (49)	114 (86)	<0·0001
IPI risk group			<0·0001			0·005
Low	31 (40)	0 (0)		31 (30)	15 (11)	
Low-intermediate	17 (22)	8 (29)		25 (24)	46 (35)	
High-intermediate	18 (23)	11 (39)		29 (28)	44 (33)	
High	11 (14)	9 (32)		20 (19)	28 (21)	

CALGB, Cancer and Leukemia Group B; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

the ≥60-year-old group (three infection, one CNS bleeding event and one pulmonary failure). Among the ≥60-year-old cohort of 28 patients, 11 (39%) completed all seven cycles as compared with 83% of those under 60 years of age; the older patients had higher rates of ending therapy for adverse events, withdrawal, or early death compared to the younger cohort (57% vs. 12%). Only two (1·9%) patients overall did not complete therapy due to early progression – one in each age cohort. Three enrolled patients were withdrawn early because one was determined to have a different lymphoma, one was HIV-positive and one underwent an allogeneic transplantation as soon as a CR was achieved.

Data were available from all patients to assess toxicity. The most common clinically significant toxicities are listed in Table III. Grade 4 neutropenia still occurred in most patients. Severe (≥grade 3) febrile neutropenia or documented bacterial infection occurred at least once in 98 patients (93%). Mucositis or stomatitis was common (69% of patients had grade 3+), and 30% had grade 3+ nausea, vomiting or diarrhoea. Renal insufficiency was seen in 10% of patients; 8% had tumour lysis syndrome, but none was life-threatening. Nineteen patients (18%) had grade 3+ pulmonary adverse events from a variety of causes, though primarily described as dyspnea/hypoxia, upper respiratory toxicity (not otherwise specified), pneumonitis or pleural effusions. Motor or sensory neuropathies or confusion were reported in 25% of patients: grade 3 sensory in eight patients, grade 3 motor in four patients, and grade 3 confusion in four patients with one grade 4. While isolated cases of seizures, behavioral changes and mood disorders were also encountered, no late onset leucoencephalopathy was reported.

Response and survival

The overall CR rate was 83% (87/105) [95% confidence interval (CI) 74–90] and there was no significant difference in the CR rate for younger adults (86%, 95% CI, 76–93) *versus* those aged 60 years or older (75%, 95% CI, 55–89). Currently, 77 (73%) patients remain in remission on long-term follow up (81% of those under 60 and 54% of those ≥60 years old, $P = 0{\cdot}002$). At 2 years, the EFS was 78% (95% CI, 69–85) and OS was 80% (95% CI, 71–86). Ten patients (10%) progressed after attaining a remission and subsequently received various therapies; seven died due to disease with a median post-relapse survival of 1 year. Outcomes were better for the younger cohort of patients (Table IV). CNS relapses were noted in only four patients, two with low/intermediate and two with high IPI risk scores; none of these were in the group of 14 patients with CNS disease at study entry. Information on Ki-67 expression was available for 72 patients: four were <90% and seven were equal to 90%. In this small group of lower expressing patients, there was no clear difference in remission rates or outcomes when compared to the higher expressing group. Overall, the survival curves plateaued approximately 2 years

Table III. Maximum toxicities reported per patient for entire treatment course.

	Patients, n (%)						
	Grade 3 (severe)		Grade 4 (life-threatening)		Grade 3–5		*P-value
Toxicity	<60 years	≥60 years	<60 years	≥60 years	<60 years	≥60 years	
Infection or febrile neutropenia	58 (75)	19 (68)	13 (17)	4 (14)	72 (94)	26 (93)	1·000
Mucositis, stomatitis, oesophagitis	40 (52)	15 (54)	10 (13)	7 (25)	50 (65)	22 (79)	0·24
Gastrointestinal (non-mucous membrane associated)	20 (26)	8 (29)	2 (3)	2 (7)	22 (29)	10 (36)	0·48
Hepatobiliary	27 (35)	6 (21)	1 (1)	1 (4)	28 (36)	7 (25)	0·35
Renal	4 (5)	5 (18)	1 (1)	1 (4)	5 (6)	6 (21)	0·06
Pulmonary	7 (9)	3 (11)	6 (8)	1 (4)	14 (18)	5 (18)	1·00
Cardiac/circulatory	6 (8)	4 (14)	5 (6)	4 (14)	11 (14)	8 (29)	0·15
Metabolic	32 (42)	14 (50)	11 (14)	7 (25)	43 (56)	21 (75)	0·11
Dermatological	9 (12)	5 (18)	1 (1)	0	10 (13)	5 (19)	0·54
Neurological	14 (18)	11 (39)	1 (1)	0	15 (19)	11 (39)	0·045
Haemorrhage	13 (17)	4 (14)	0	0	13 (17)	5 (18)	1·00

To avoid duplicate counting of events within these categories and to keep the categories mutually exclusive, the following definitions were used: (i) Infection includes all infections under the category of infection, including febrile neutropenia. (ii) Mucositis, stomatitis, oesophagitis includes just these events. (iii) Gastrointestinal includes all other AEs under the gastrointestinal category, excluding mucositis, stomatitis and oesophagitis.
*P-value for the differences in grade 3–5 toxicities between age cohorts.

Table IV. Response evaluation by age group and for all patients on CALGB studies 10 002 and 9251; and by IPI category.

	<60 years	≥60 years	CALGB 10 002	CALGB 9251
Patients (*n*)	77	28	105	133
Complete response (95% CI)	86% (76, 93)	75% (55, 89)	83% (74, 90)	69% (61, 77)
Current status of all patients				
Continuous remission	62 (80%)	15 (54%)	77 (73%)	58 (44%)
Treatment-related death	2 (3%)	5 (18%)	7 (7%)	15 (11%)
Died from progressive disease	9 (12%)	7 (25%)	16 (15%)	54 (41%)
Died from another cause	4 (5%)	1 (3%)	5 (5%)	6 (5%)
2-year probability EFS (95% CI)	0·87 (0·77, 0·93)	0·54 (0·34, 0·70)	0·78 (0·69, 0·85)	0·49 (0·40, 0·57)
4-year probability EFS (95% CI)	0·82 (0·71, 0·89)	0·54 (0·34, 0·70)	0·74 (0·65, 0·81)	0·46 (0·38, 0·55)
2-year probability OS (95% CI)	0·87 (0·77, 0·93)	0·61 (0·40, 0·76)	0·80 (0·71, 0·86)	0·57 (0·48, 0·65)
4-year probability OS (95% CI)	0·84 (0·74, 0·91)	0·61 (0·40, 0·76)	0·78 (0·69, 0·85)	0·52 (0·43, 0·60)
Hazard Ratio		3·0 (1·4, 6·3)		

	CALGB 10 002		CALGB 9251	
IPI Category	4-year probability EFS (95% CI)	4-year probability OS (95% CI)	4-year probability EFS (95% CI)	4-year probability OS (95% CI)
Low	0·86 (0·67, 0·95)	0·90 (0·72, 0·97)	0·67 (0·38, 0·85)	0·73 (0·44, 0·89)
Low-intermediate	0·80 (0·58, 0·91)	0·88 (0·67, 0·96)	0·56 (0·41, 0·69)	0·65 (0·49, 0·77)
High-intermediate	0·69 (0·49, 0·82)	0·72 (0·52, 0·85)	0·36 (0·22, 0·50)	0·39 (0·24, 0·52)
High IPI	0·55 (0·31, 0·73)	0·55 (0·31, 0·73)	0·35 (0·19, 0·53)	0·39 (0·22, 0·57)

CALGB, Cancer and Leukemia Group B; IPI, International Prognostic Index; EFS, event-free survival; OS, overall survival; 95% CI, 95% confidence interval.

after completing treatment, with few relapses following this time point. Though outcomes were encouraging for all groups, response rates and survival endpoints differed significantly according to IPI risk criteria ($P < 0{\cdot}0001$), with higher risk patients having worse EFS and OS (Table IV and Fig 1A, B). Nevertheless, over half of these high risk patients were long term survivors. The 4-year EFS and OS for 31 patients with low IPI scores were 86% and 90%, respectively.

In focusing on the 58 patients with material submitted and confirmed to be BL using current criterion, the 2-year EFS and OS was 79% (95% CI, 66–88) and 81% (95% CI, 68–89) respectively. The 25 with other high risk lymphoma based on central pathology review had a slightly lower 2-year EFS and OS [64%; (95% CI, 42–79) for both].

Comparison with prior 'chemotherapy only' results

These data compare favourably with our prior study for a similar adult patient population, CALGB 9251 (Rizzieri *et al*, 2004). It is important to note in this retrospective comparison that our prior study involved more patients with an elevated lactate dehydrogenase (LDH) or advanced stage disease and thus a slightly higher overall IPI risk grouping (Table II). With the current study's addition of growth factor support and immunotherapy, similar rates of treatment-related mortality (TRM) were noted (9% compared to 13%). Response rates, EFS and OS improved when comparing across IPI risk groups (Table IV and Fig 1C).

A number of Cox proportional hazards models were fit to determine the best model. Inclusion of the individual factors in the IPI resulted in a better model than the summary risk category. The risk factors included in the model were age as a continuous variable and categorical variables coded 0, 1 indicating more than one extra-nodal site, advanced stage of disease, performance status >1, elevated LDH and study. After adjustment for these factors, the hazard ratio was 0·38, indicating a marked reduction in risk using the current CALGB 10 002 regimen ($P = 0{\cdot}0001$; data not shown).

Discussion

Burkitt lymphoma responds well to intensive chemotherapy that includes high doses of antimetabolites and alkylating agents delivered in a dose dense fashion (Murphy *et al*, 1986; Hann *et al*, 1990; McMaster *et al*, 1991; Schwenn *et al*, 1991; Larson *et al*, 1995; Magrath *et al*, 1996). However, relapses still occur and treatment-related toxicities have made this approach infeasible for many older patients. Applying the principles of chemo-immunotherapy is attractive in this disease given the high expression of CD20 and improved outcomes seen in other lymphomas and a single agent 'window study' in Burkitt lymphoma (Meinhardt *et al*, 2010). Thus, this study evaluated three modifications to our prior regimen – the addition of rituximab, primary prophylaxis with filgrastim and the elimination of prophylactic cranial radiation. Results are encouraging, with a high rate of study completion, high remission rates and encouraging long term

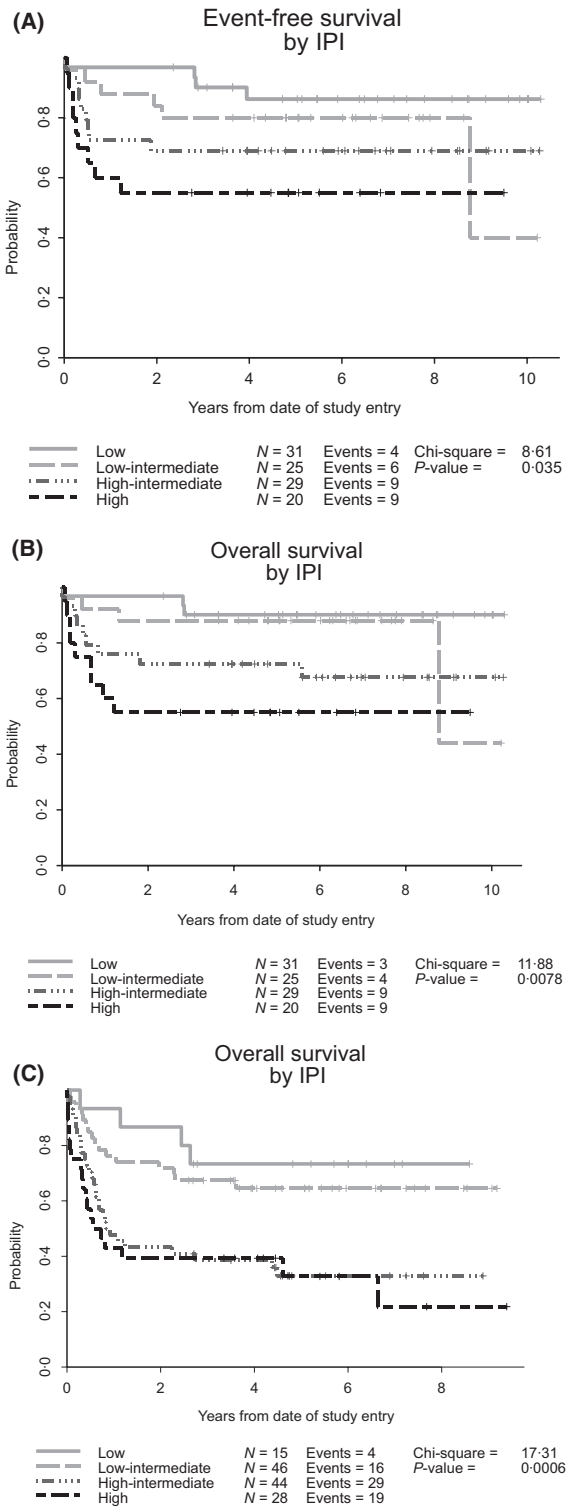

Fig 1. Event-free (A) and overall survival (B) for all patients stratified by IPI criteria in CALGB 10 002 and overall survival for all patients stratified by IPI criteria in CALGB 9251 (C). Though developed for diffuse large B-cell lymphoma, the IPI was found to predict outcomes for our patients with BL as well. The addition of rituximab appears to improve outcomes compared to the prior regimen (CALGB 9251) without. CALGB, Cancer and Leukemia Group B; IPI, International Prognostic Index.

survival. We found that the IPI was highly predictive of long-term outcome in this cohort of BL patients. Of note, those under 60 years of age trended to a higher remission rate than those 60 years of age or older, though this was not statistically significant. What was significant was the increased durability of remission in the younger *versus* older population (81% vs. 54%), possibly indicating a different biology in Burkitts disease in older patients, as is noted in other hematopoietic malignancies (Rao *et al*, 2009) or the importance of the higher proportion of subjects in the younger age group completing the entire dose dense therapy protocol.

These data should be interpreted in light of our evolving understanding of BL and other high risk, aggressive non-Hodgkin lymphomas. As the diagnosis has always been made from a constellation of morphology, immunophenotyping and cytogenetics, discordance between haematopathologists has been a well-recognized concern (Rizzieri *et al*, 2004). Our evolving understanding of the illness has led the most current WHO classification schema (Leoncini *et al*, 2008) to be more restrictive in the diagnosis of BL, while deleting the 'Burkitt-like' designation in use at the time this study was implemented. The WHO recognizes that still there are cases in which diagnosis of BL *versus* other aggressive lymphomas is controversial and in these cases the aggressive non-Burkitt lymphomas (including, but not limited to, 'double' or 'triple hit' lymphomas) are typically treated as BL, though optimal treatment remains to be determined (Leoncini *et al*, 2008). Our study includes such patients based on the current definitions in use. However, a separate analysis of the 58 subjects with material submitted and confirmed to be BL with the current classification system revealed outcomes similar to the whole group of 105 patients, while those with other high risk diseases seem to fare a bit worse, though the subgroups are small.

Common antimetabolite-containing regimens, such as CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine), yield good results in this disease; however, most experience has been reported with children or young adults (Magrath *et al*, 1996; Mead *et al*, 2002). Notably, lowering the dose of methotrexate to 3 g/m^2 was associated with poor results for intermediate and high risk patients (2-year EFS 49%) (Mead *et al*, 2008). While there has been a retrospective analysis of adding rituximab to a CODOX-M/IVAC type backbone that was discouraging (Barnes *et al*, 2011), prospective chemo-immunotherapy studies have recently been completed and report the addition of rituximab to a modified CODOX-M/IVAC backbone has very encouraging results (Corazzelli *et al*, 2012; Evens *et al*, 2013). Further, Dunleavy *et al* (2013) reported preliminary data on the use of 'DA-EPOCH-R' (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) in patients with *MYC*-positive diffuse large cell or Burkitt lymphoma, noting 97% EFS. The use of rituximab and younger patient age were

both associated with improved outcomes in these studies, and also seen in our report. The populations in the above studies were similar to ours, though the overall small size of the studies did not allow breakdown by IPI categorization, as we have, to allow a more direct comparison. Kasamon *et al* (2013) recently published a small report focused on adults and the use of high dose, alkylator and rituximab-based therapy for higher risk patients. This group noted that induction followed by high dose cyclophosphamide therapy (but not using stem cell support), followed by maintenance, resulted in a 3-year overall survival of 57%, comparable to our high risk group however TRM was high (24%) (Kasamon *et al*, 2013). Ferreri *et al* (2012) reported the results of a similar dose intense, short course, chemoimmunotherapy induction followed by high dose alkylator-based therapy (requiring stem cell support for many) focusing on adults with Burkitts disease associated with HIV virus. Again the chemo-immunotherapy combination proved tolerable with high rates of response and 11 of 15 remaining progression-free at 2 years follow-up (Ferreri *et al*, 2012). The Northern Italian Leukaemia Group recently published results for adult Burkitt patients using a similar backbone of chemoimmunotherapy as our current study, noting a high TRM of 18% but similar long term outcome with 67% 3-year OS, with marked differences based on IPI status, as we have also shown (Intermesoli *et al*, 2013). Similarly, Hoelzer *et al* (2012) presented preliminary results of a similar approach in a cohort of 363 adults, in which they noted that chemoimmunotherapy was well tolerated and resulted in high response rates although, commensurate with our data, results in high risk IPI patients remained less encouraging.

In order to assess the added benefit of the combination of immunotherapy and chemotherapy in the adult population, we compared the results from CALGB 10 002 with our prior study, CALGB 9251, which used a nearly identical chemotherapeutic approach but without the use of the monoclonal antibody. CALGB 9251 also used more intensive CNS prophylaxis than now appears necessary as well as less cytarabine. While the treatment groups were similar in these two studies, there was a trend to more low risk patients in the current study (30% vs. 11%). Although the TRM was similar, the current study resulted in a higher proportion of patients completing at least six cycles of therapy (77% vs. 65%) and fewer patients progressing while on study (2% vs. 14%). Improved outcomes with the CALGB 10 002 regimen were also noted when comparing within individual IPI risk categories (Table IV and Fig 1). In a multivariate analysis adjusting for risk factors, treatment on the current CALGB 10 002 chemo-immunotherapy regimen improved survival compared with the prior regimen of CALGB 9251 (hazard ratio 0·38, H 0·0001), supporting the use of chemo-immunotherapy for BL in adults. However, only a randomized, prospective study can truly validate this conclusion.

There is still room for improvement in older patients, who experience a higher rate of adverse events, and in those who are high risk by IPI criteria. Newer therapies targeting cell surface antigens other than CD20 or dysregulated B-cell receptor or intracellular pathways have been effective in other haematological malignancies. Bruton's tyrosine kinase inhibition in CLL (Herman *et al*, 2011; Ponader *et al*, 2012), CD22 targeting with an immunoconjugate, such as inotuzumab ozogamicin (Advani *et al*, 2010), CD19 targeting chimeric antigen receptors or T-cell engaging bi-specific antibodies, such as blinatumomab (Topp *et al*, 2011), are encouraging in their early data and merit exploration in these patients.

Acknowledgements

The research for CALGB 10 002 (Alliance) was supported, in part, by grants from the National Cancer Institute (CA31946) to the Alliance for Clinical Trials in Oncology (Monica M. Bertagnolli, M.D., Chair) and to the Alliance Statistics and Data Center (Daniel J. Sargent, Ph.D., CA33601). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

The following institutions participated in this study: Christiana Care Health Services, Inc. CCOP, Wilmington, DE, Stephen Grubbs, M.D., supported by CA45418. Dana-Farber Cancer Institute, Boston, MA, Harold J. Burstein, M.D., Ph.D., supported by CA32291. Duke University Medical Center, Durham, NC, Jeffrey Crawford, M.D., supported by CA47577. Monter Cancer Center of North Shore – LIJ Health Systems, Lake Success, NY, Daniel Budman, MD, supported by CA35279. Rhode Island Hospital, Providence, RI, William Sikov, M.D., supported by CA08025. Roswell Park Cancer Institute, Buffalo, NY, Ellis Levine, M.D., supported by CA59518. The Ohio State University Medical Center, Columbus, OH, Clara D. Bloomfield, M.D., supported by CA77658. University of California at San Diego, San Diego, CA, Barbara A. Parker, M.D., supported by CA11789. University of Chicago, Chicago, IL, Hedy L. Kindler, M.D., supported by CA41287. University of Illinois MBCCOP, Chicago, IL, David J. Peace, M.D., supported by CA74811. University of Iowa, Iowa City, IA, Daniel A. Vaena, M.D., supported by CA47642. University of Maryland Greenebaum Cancer Center, Baltimore, MD, Martin Edelman, M.D., supported by CA31983. University of Minnesota, Minneapolis, MN, Bruce A. Peterson, M.D., supported by CA16450. University of North Carolina at Chapel Hill, Chapel Hill, NC, Thomas C. Shea, M.D., supported by CA47559. University of Vermont, Burlington, VT, Steven M. Grunberg, M.D., supported by CA77406. Wake Forest University School of Medicine, Winston-Salem, NC, David D. Hurd, M.D., supported by CA03927.

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Conflicts of interest

The authors report there are no reported conflicts of interest related to this study.

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