Intensive Chemotherapy with and without Cranial Radiation for Burkitt Leukemia and Lymphoma

Final Results of Cancer and Leukemia Group B Study 9251

David A. Rizzieri[1]
Jeffrey L. Johnson[2]
Donna Niedzwiecki[2]
Edward J. Lee[3]
James W. Vardiman[4]
Bayard L. Powell[5]
Maurice Barcos[6]
Clara D. Bloomfield[7]
Charles A. Schiffer[8]
Bruce A. Peterson[9]
George P. Canellos[10]
Richard A. Larson[4]

[1] Department of Medicine, Duke University Medical Center, Durham, North Carolina.

[2] Cancer and Leukemia Group B Statistical Center, Durham, North Carolina.

[3] Maryland Oncology, PA, Columbia, Maryland.

[4] Department of Pathology, University of Chicago, Chicago, Illinois.

[5] Department of Hematology and Oncology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina.

[6] Department of Pathology, Roswell Park Cancer Institute, Buffalo, New York.

[7] Department of Hematology and Oncology, College of Medicine and Public Health, The Ohio State University, Columbus, Ohio.

[8] Department of Internal Medicine, School of Medicine, Wayne State University, Detroit, Michigan.

[9] Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

[10] Dana-Farber Cancer Institute, Boston, Massachusetts.

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BACKGROUND. The objective of the current study was to evaluate the efficacy of intensive chemotherapy with and without cranial radiation for central nervous system (CNS) prophylaxis in adults with Burkitt leukemia or lymphoma.

METHODS. Patients received 18 weeks of therapy. Prophylactic cranial radiation (2400 centigrays) and 12 doses of triple intrathecal chemotherapy were administered to the first cohort of patients. A subsequent cohort received the same therapy, with the exceptions that intrathecal therapy was reduced to six doses and radiotherapy was administered only to high-risk individuals.

RESULTS. The median follow-up durations were 6.8 years in Cohort 1 and 4.1 years in Cohort 2. Three occurrences of transverse myelitis, 2 severe neuropathies, 3 cases of aphasia, and 1 case of blindness were documented in the first cohort of 52 patients (Cohort 1). In the subsequent cohort of 40 patients (Cohort 2), none of these occurrences were observed, and patients experienced less neurologic toxicity overall (61% vs. 26%; $P = 0.001$). Responses were similar, and the 3-year event-free survival rate was 0.52 (95% confidence interval, 0.38–0.65) for Cohort 1 and 0.45 (0.29–0.60) for Cohort 2.

CONCLUSIONS. Intensive, short-duration chemotherapy with less intensive CNS prophylaxis led to control at this sanctuary site with little neurotoxicity and may be curative for adults with Burkitt leukemia or lymphoma. ***Cancer* 2004;100:1438–48.**
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KEYWORDS: Burkitt leukemia, Burkitt lymphoma, chemotherapy, central nervous system prophylaxis non-Hodgkin lymphoma, small noncleaved cell lymphoma.

Address for reprints: David A. Rizzieri, Department of Medicine, Division of Oncology and Bone Marrow Transplantation, Box 3961, Duke University Medical Center Durham, NC 27710; Fax: (919) 668-1091; E-mail: rizzi003@mc.duke.edu

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Burkitt lymphoma is a highly aggressive malignancy that often presents at extranodal sites or as an acute leukemia (Burkitt leukemia) composed of monomorphic, medium-sized B cells with basophilic cytoplasm and numerous mitotic figures. Chromosomal translocation leading to overexpression of *MYC* and a growth fraction of nearly 100% are constant genetic features. Previous classification systems have included this distinctive neoplasm among the small noncleaved cell (SNC) non-Hodgkin lymphomas (NHL), which represent 2–3% of all NHLs.[1] The distinction between Burkitt lymphoma and Burkitt leukemia (previously known as L3 acute lymphoblastic leukemia [ALL] using the French–American–British [FAB] classification system) is largely semantic, because these malignancies share immunophenotypic and cytogenetic features.[2,3] Each typically has an initial high response rate, but early progression frequently occurs after standard chemotherapy regimens commonly used either for diffuse large cell lymphoma or for precursor B-cell ALL. The similarities in diagnosis and treatment for patients with a World Health Organization classification of Burkitt leukemia or lymphoma justify the inclusion of these patients in a single category for the evaluation of efficacy, as was done in the current report.[4]

Previous studies have shown that aggressive combination chemotherapy using high doses of antimetabolites and alkylating agents over a short duration was effective in children and adults with Burkitt leukemia and lymphoma.[5–7] In Cancer and Leukemia Group B (CALGB) study 9251, the CALGB modified the previously reported German Multicenter ALL Group (GMALL) regimen, which used 18 weeks of intensive chemoradiotherapy; preliminary results were encouraging, but the central nervous system (CNS) toxicity of the combined-modality therapy was unacceptable.[7,8] This prompted treatment of a second group of patients in a similar manner but with decreased prophylaxis for the CNS. The current report provides the final analysis for the 92 eligible patients with confirmed Burkitt leukemia or lymphoma who were treated on this study, detailing toxicities, response rates, and long-term efficacy and comparing the first and second sequential cohorts. It is noteworthy that we have shown that less extensive CNS prophylaxis decreases severe neurotoxicity and yet maintains the efficacy of this intensive, short-duration approach.

MATERIALS AND METHODS:

Previously untreated patients age $\geq$ 15 years were enrolled on the current study if they had been diagnosed by the local pathologist with high-grade small noncleaved cell NHL (Category J in the International Working Formulation) or FAB L3 ALL. Confirmation of Burkitt leukemia or lymphoma was required on central pathology review. Patients known to be positive for human immunodeficiency virus were excluded. Total bilirubin and serum creatinine levels $\leq$ 1.5 times the upper limit of normal were required unless directly attributable to disease. Leukemia was defined by $>$ 25% involvement of the bone marrow. Each local Institutional Review Board approved the study protocol. All patients provided written informed consent.

Central Review of Diagnosis

Slides from tumor biopsies and bone marrow aspirates from all patients were to be reviewed by the CALGB Pathology Committee (M.B. and J.W.V.). Immunophenotyping results often were available, but Ki-67 staining was not. Patients also were enrolled on CALGB study 8461, a prospective analysis of karyotypes.

Statistical Methods

The study was designed with an early stopping rule (applicable to the first cohort reported in the current article) to test the null hypothesis that the complete remission (CR) rate was $\leq$ 0.60 versus the alternative that the CR rate was $\geq$ 0.80 with 90% power ($\alpha = 0.05$). Overall survival (OS) was measured from study entry to death due to any cause or to the date on which the patient was last known to be alive. Event-free survival (EFS) was measured from enrollment to the date of treatment failure or to the date on which the patient was last known to be alive. Treatment failure was defined in the current trial as progressive disease, death due to any cause, or removal from protocol therapy without response. Disease-free survival (DFS) was measured from the date of achievement of CR to the date of recurrence or death or to the date on which the patient was last known to be alive.

Regression analysis of the patient and disease characteristics detailed in Table 1 was used to evaluate predictors of response, EFS, DFS, and OS. Survival function estimates were computed using the product-limit method, and survival distributions were compared using the log-rank test.[9]

Treatment Regimen

The treatment regimen is shown in Table 2 and has been described in detail previously.[8] The modifications for intrathecal chemotherapy and cranial radiotherapy implemented after the first cohort of patients were treated also are shown. The initial cohort of 52 patients (Cohort 1) received triple intrathecal therapy twice per cycle during Cycles 2–7 (12 total doses) plus 12 daily doses of prophylactic cranial radiotherapy

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%) Cohort 1 (n = 52)	Cohort 2 (n = 40)	P value	Total no. (%) (n = 92)
Age (yrs)				
Median	44	50	0.63	47
Range	18–72	17–78	—	17–78
No (%) age ≥ 60 yrs	10 (19)	9 (23)	0.80	19 (21)
Male	34 (65)	32 (80)	0.16	66 (72)
Race/ethnicity				
White	48 (92)	34 (85)	0.37	82 (89)
Hispanic	0 (0)	1 (2)	—	1 (1)
Black	4 (8)	3 (7)	—	7 (8)
Other	0 (0)	2 (5)	—	2 (2)
Performance status (CALGB)[a]				
0	9 (17)	6 (15)	0.52	15 (16)
1	28 (54)	19 (49)	—	47 (52)
2	10 (19)	8 (21)	—	18 (20)
3	3 (6)	6 (15)	—	9 (10)
4	2 (4)	0 (0)	—	2 (2)
B symptoms	29 (56)	23 (59)	0.83	52 (57)
Extranodal sites (lymphoma group)				
0	7 (23)	8 (50)	0.22	15 (33)
1	10 (33)	4 (25)	—	14 (30)
2+	13 (43)	4 (25)	—	17 (37)
Extramedullary sites (leukemia group)				
0	5 (23)	7 (29)	0.60	12 (26)
1	9 (41)	6(25)	—	15 (33)
2+	8 (36)	11 (46)	—	19 (41)
Lymph node involvement	46 (88)	28 (70)	0.04[b]	74 (80)
Bone marrow involvement	31 (60)	27(68)	0.50	58 (63)
Elevated LDH (> ULN)	47 (90)	33 (83)	0.35	80 (87)
CNS involvement	2 (4)	3 (7)	0.65	5 (5)
Lymphoma stage				
I	4 (13)	2 (12)	1.00	6 (13)
II	3 (10)	1 (6)	—	4 (9)
III	6 (20)	3(19)	—	9 (20)
IV	39 (75)	34 (85)	—	73 (79)
IPI risk group				
Low	5 (10)	4 (10)	0.03	9 (10)
Low-int	22 (42)	11 (28)	—	33 (36)
High-int	11 (21)	20 (50)	—	31 (34)
High	14 (27)	5 (12)	—	19 (21)

CALGB: Cancer and Leukemia Group B; LDH: lactate dehydrogenase; ULN: upper limit of normal; int: intermediate; CNS: central nervous system; IPI: International Prognostic Index.

[a] One patient with leukemia in Cohort 2 did not have a performance status recorded.

[b] More patients with leukemia were enrolled in Cohort 2, accounting for the smaller percentage of patients with lymph node involvement.

TABLE 2
Treatment Schema

Cycle 1
- Cyclophosphamide: 200 mg/m^2/day IV on Days 1–5
- Prednisone: 60 mg/m^2/day orally on Days 1–7

Cycles 2, 4, and 6
- Ifosfamide: 800 mg/m^2 day IV over 1 hr on Days 1–5
- Mesna: 200 mg/m^2/day IV at 0, 4, and 8 hrs after ifosfamide
- Methotrexate: 150 mg/m^2 IV over 30 min, then 1.35 g/m^2 IV over 23.5 hrs (total dose, 1.5 gm/m^2)
- Leucovorin[a]: 50 mg/m^2 IV 36 hrs after initiation of methotrexate, then 15 mg/m^2 every 6 hrs
- Vincristine: 2 mg IV push on Day 1
- Cytarabine: 150 mg/m^2/day by continuous infusion on Days 4 and 5
- Etoposide: 80 mg/m^2/day IV over 1 hr on Days 4 and 5
- Dexamethasone: 10 mg/m^2 orally on Days 1 through 5

Cycles 3, 5 and 7
- Cyclophosphamide: 200 mg/m^2/day IV on Days 1–5
- Methotrexate: 150 mg/m^2 IV over 30 min, then 1.35 g/m^2 IV over 23.5 hrs (total dose, 1.5 g/m^2)
- Leucovorin[a]: 50 mg/m^2 IV starting 36 hrs after initiation of methotrexate, then 15 mg/m^2 every 6 hrs
- Vincristine: 2 mg IV push
- Doxorubicin: 25 mg/m^2/day IV bolus on Days 4 and 5
- Dexamethasone: 10 mg/m^2 orally on Days 1–5
- Intrathecal chemotherapy with Cycles 2–7

Preamendment[b]
- Methotrexate: 15 mg on Days 1 and 5
- Cytarabine: 40 mg on Days 1 and 5
- Hydrocortisone: 50 mg on Days 1 and 5
- Cranial irradiation: 2400 cGy administered in 12 fractions after Day 5 of Cycle 3 and before the start of Cycle 4

Postamendment
- Methotrexate: 15 mg on Day 1
- Cytarabine: 40 mg on Day 1
- Hydrocortisone: 50 mg on Day 1
- Cranial irradiation: 2400 cGy administered in 12 fractions after chemotherapy for Cycle 7 was completed, but only for patients who had prior bone marrow disease

IV: intravenous; Mesna: sodium mercaptoethanesulfonate; cGy: centigrays.

[a] Leucovorin was continued until the methotrexate concentration was measured to be < 0.05 μM.

[b] The protocol was amended after the first 52 eligible patients were treated to decrease central nervous system prophylaxis for patients who were not considered to be at high risk.

(total, 2400 centigrays [cGy]) between Cycles 3 and 4. Whole-brain radiation included the posterior half of the orbit and extended to the second cervical vertebral body. The second cohort of 40 patients (Cohort 2) received only 1 dose of intrathecal therapy per cycle in Cycles 2–7 (6 total doses) and received cranial radiation only after the completion of all chemotherapy if they had had high-risk disease (defined as bone marrow involvement) at the time of diagnosis. All patients with CNS involvement at diagnosis were started immediately on weekly triple intrathecal chemotherapy concomitant with systemic chemotherapy until the cerebrospinal fluid (CSF) was clear, and then weekly for 4 doses, followed by 2400 cGy cranial radiation.

Evaluation and Response Criteria

Toxicity was monitored in all patients using the CALGB Expanded Common Toxicity Criteria. Toxicity is reported as the most severe event per organ site for each patient throughout the entire treatment period. Assessment of all known areas of disease was required to define response. Radiographic scans of the chest,

abdomen, pelvis, and other known areas of disease in patients with lymphoma were required after every two courses of therapy, in addition to bone marrow examinations for patients with leukemia. Remission for patients with leukemia or lymphoma required the disappearance of all disease on examination, radiographic studies, and bone marrow evaluation for at least 4 weeks. If a tumor mass was active on a functional study performed before therapy (e.g., gallium scanning), then the functional study had to be repeated and was required to be negative for a CR. Patients who had leukemia plus lymph node disease also were evaluated using the same criteria that were used for patients who had lymphoma. A partial response (PR) required a reduction $>$ 50% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions that lasted $>$ 4 weeks, during which no new lesions appeared and no existing lesions enlarged. Disease progression or recurrence was defined as an increase in the sum of the products of the 2 greatest perpendicular dimensions of any measurable lesion by $>$ 25% relative to the size at study entry, the appearance of new areas of malignancy, or the recurrence of lymphoblasts in the bone marrow or blood.

RESULTS

Patient Characteristics

One hundred thirty-three patients (83 with lymphoma and 50 with leukemia) were enrolled on CALGB study 9251 between May 12, 1992, and February 29, 2000, from 22 main member institutions and their affiliated hospitals. No single center enrolled $>$ 10% of the patients. Two enrolled patients who had leukemia did not have central pathology review, and 2 patients (4%) who had central pathology review were believed to have ALL pathology other than Burkitt leukemia. One patient with SNC lymphoma was ineligible because of the receipt of CNS radiotherapy just prior to initiation of treatment. Another enrolled patient was found not to have had Burkitt lymphoma before beginning to receive treatment and thus was withdrawn from the study. Eight enrolled patients with lymphoma did not have central pathology review, and 27 of 73 remaining patients with lymphoma who had central pathology review had discordant diagnoses. The most common alternative diagnosis provided by central pathology review was diffuse large cell lymphoma (n = 18), followed by immunoblastic lymphoma (n = 4), follicular lymphoma (n = 2), unclassifiable lymphoma (n = 2), and mantle cell lymphoma (n = 1). Thus, 92 patients met all eligibility criteria after central pathology review and were included in the current analysis, including 46 patients with lymphoma and 46 patients with leukemia. The median follow-up for survivors was 6.8 years (range, 3.4–9.4 years) for the 51 patients in Cohort 1 and 4.1 years (range, 2.3–5.2 years) for the 41 patients in Cohort 2.

Karyotypes from bone marrow cytogenetic specimens were adequate on central review from 19 patients with lymphoma. Thirteen karyotypes were normal, although 5 patients had morphologic bone marrow involvement. Four karyotypes had t(8;14)(q24;q32) or one of its variants, and one karyotype had $-$Y and another had t(11;19)(q23;p13.3) as their lone clonal abnormalities. Among 32 centrally reviewed and evaluable patients with Burkitt leukemia, 22 patients had a typical t(8;14) or one of its variants, 5 patients had normal karyotypes, and 5 patients had other abnormalities. Thus, in total, 26 patients had a typical t(8;14), t(8;22)(q24;q11), or t(2;8)(p12;q24) abnormality detected.

The median age of the 52 patients in Cohort 1 was 44 years (range, 18–72 years), with 10 patients age $>$ 60 years, whereas the median age of the 40 patients in Cohort 2 was 50 years (range, 17–78 years), with 9 age $>$ 60 years (Table 1). The patient characteristics did not differ by disease presentation of lymphoma or leukemia (data not shown). Evaluation of the prognostic factors used in calculating the International Prognostic Index (IPI) for lymphomas[10] revealed that there were more high-intermediate-risk or high-risk patients in Cohort 2 compared with Cohort 1 (62% vs. 48%), due in part to the larger proportion of patients with leukemia (Stage IV) enrolled in Cohort 2.

Treatment Delivery and Toxicity

Data were available for the assessment of treatment toxicity in 91 of 92 patients. There were no significant differences between the patients in Cohort 1 and those in Cohort 2 regarding the percentage of patients who completed all planned therapy (56% vs. 58%, respectively; P = 1.00). Excluding patients who were withdrawn due to progressive disease, 69% and 72% of patients in Cohorts 1 and 2, respectively, completed all 7 cycles of therapy (Table 3). Fewer patients age $>$ 60 years were able to complete therapy compared with younger patients (26% vs. 64%; P = 0.004). There was no significant difference in the number of cycles received by patients with Burkitt lymphoma or leukemia (data not shown).

All patients had Grade 3 or 4 myelosuppression. Grade 3 or greater infection occurred in 85% of patients in Cohorts 1 and 2 alike: 3 patients (6%) in Cohort 1 and 4 patients (10%) in Cohort 2 died of infection (Table 4). Renal insufficiency was not uncommon: 27% of patients in Cohort 1 and 33% of patients in Cohort 2 had Grade 3 or 4 renal toxicity, but there were no fatal complications. Mucositis and

TABLE 3
Numbers and Percentages of Patients who Completed Each Treatment Cycle and Reasons for Stopping Treatment

	Cohort 1		Cohort 2	
Cycle completed	Total no. (%)	Reason treatment ended	Total no. (%)	Reason treatment ended
1	52 (100)	1 D, 1 WD	40 (100)	2 D, 1 WD
2	50 (96)	2 D	37 (93)	2 D
3	48 (92)	1 PD, 1 D	35 (88)	2 PD, 1 T, 1 D, 1 WD
4	46 (88)	2 PD, 1 T, 3 D, 1 WD	30 (75)	3 PD, 1 T, 1 WD
5	39 (75)	2 PD, 1 T, 1 WD	25 (63)	1 PD
6	35 (67)	2 PD, 4 T	24 (60)	1 WD
7	29 (56)	29[b]	23 (58)	23[b]

D: death; WD: physician decision or patient withdrawal of consent to proceed; PD: progressive disease; T: toxicity.

[a] Overall, only 56% and 58% of patients completed all 7 courses of therapy in Cohorts 1 and 2, respectively. If patients who were withdrawn early due to PD are not included, then 69% and 72% of patients, respectively, were able to complete all 7 cycles.

[b] These patients completed therapy.

stomatitis were extremely common, although they were less common in Cohort 2. Furthermore, 67% of patients in Cohort 1 and 41% of patients in Cohort 2 had Grade 3–4 toxicity of the gastrointestinal system ($P = 0.02$). There were significantly fewer severe rashes and other dermatologic toxicities in Cohort 2 compared with Cohort 1 ($P = 0.006$). Despite receiving appropriate supportive care, including hydration and allopurinol administration, three patients (one in Cohort 1 and two in Cohort 2) had fatal metabolic abnormalities due to tumor lysis syndrome.

Neurologic complications were common in Cohort 1. Twenty-seven patients (52%) in Cohort 1 who had Grade 3 or 4 neurologic complications (8%) had Grade 4 neurologic impairment. It is noteworthy that in this cohort, 11 patients (21%) reported severe sensory problems, resulting primarily from paresthesias, dysesthesia, and numbness; 18 patients (35%) had severe motor disturbances with diffuse weakness of the upper and lower extremities; 13 patients (25%) had cortical dysfunction, with memory deficits, lethargy/stupor, and delirium reported as being the primary problems; and 3 patients (6%) had cerebellar dysfunction. None of these events were caused by new CNS lesions; instead they appeared to be due to peripheral neuropathy or diffuse central neuronal effects. Twenty-five of 27 patients with Grade 3 neurologic toxicities and 4 of 4 patients with Grade 4 neurologic toxicities had received cranial radiotherapy. The distribution of these toxicities did not differ statistically in patients age $\geq$ 60 years or age $\leq$ 60 years. No patients received spinal radiation. Three patients in Cohort 1 had transverse myelitis outside the cranial radiation field, two patients had severe peripheral neuropathy, three patients had transient aphasia, and one patient had blindness that was not transient.

Patients in Cohort 2 experienced less severe neurologic toxicity compared with patients in Cohort 1 (23% vs. 60%; $P = 0.0006$). With less intrathecal therapy administered to all patients and radiotherapy administered only to those with bone marrow involvement or active CNS disease, only 9 patients (23%) in Cohort 2 had severe neurotoxicity. Five patients (13%) in Cohort 2 had severe weakness, 2 patients had severe peripheral neuropathies, and 4 patients had cortical dysfunction. Only 1 patient (2%) in Cohort 2 had Grade 4 neural toxicity, which involved a seizure that probably was related to intrathecal therapy and ifosfamide treatment. There were no episodes of transverse myelitis or blindness in Cohort 2. To further assess the impact of the amended treatment on neurotoxicity, we analyzed patients with lymphoma who received at least three cycles of chemotherapy per protocol and were at *low risk* (i.e., they did not have bone marrow involvement and thus did not receive cranial radiotherapy after chemotherapy if they were in Cohort 2). There were 21 of these patients who were treated before the regimen was amended, compared with 11 patients in the postamendment group. The rate of Grade 3 or 4 neurotoxicity decreased significantly in the latter group (62% [Cohort 1] vs. 9% [Cohort 2]; $P = 0.0075$).

Response and Survival

Sixty-eight of 92 patients (74%) achieved a CR. Another 10 patients achieved a PR, yielding an overall response rate of 85%. Five patients with PRs had leukemia and lymph node disease. There were no significant differences noted in the response rates between the lymphoma group or the leukemia group. Seventy-nine percent of patients in Cohort 1 and 68% in Cohort 2 achieved a CR. Eighty-one percent of patients in Cohort 1 and 80% of patients in Cohort 2 achieved a CR or a PR (*P* not significant) (Table 5). Central nervous system recurrences occurred in four patients with leukemia, two from each cohort; one patient had had CNS disease at diagnosis. These data suggest that this regimen is effective in adults and that decreasing the intensity of prophylactic CNS therapy did not increase the CNS failure rate.

Figure 1A–C demonstrates the EFS, DFS, and OS curves for the 52 patients in Cohort 1 prior to the amendment and the 40 patients in Cohort 2 after the amendment. The survival curves plateau after approximately 2 years. The EFS rates (with 95% confidence intervals [95% CIs]) at 3 years were 52% (95% CI, 38–65%) for Cohort 1 and 45% (95% CI, 29–60%) for

TABLE 4
Most Common Nonhematologic Toxicities Separated by Cohort

	No. of patients (%)								
	Grade 3 (severe)		Grade 4 (life threatening)		Grade 5 (lethal)		Grade 3–5		
Toxicity	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	*P* value
Infection	33 (63)	25 (62)	8 (15)	5 (12)	3 (6)	4 (10)	44 (85)	34 (85)	1.00
Mucositis, stomatitis, esophagitis	16 (31)	18 (45)	21 (40)	10 (26)	—	—	37 (71)	28 (72)	1.00
Gastrointestinal (non–mucous membrane–associated)	20 (38)	12 (31)	15 (29)	4 (10)	—	—	35 (67)	16 (41)	0.02
Liver	19 (37)	10 (26)	7 (13)	11 (28)	—	—	26 (50)	21 (54)	0.83
Renal	9 (17)	9 (23)	5 (10)	4 (10)	—	—	14 (27)	13 (33)	0.64
Pulmonary	5 (10)	5 (13)	6 (12)	8 (21)	—	—	11 (21)	13 (33)	0.23
Cardiac/circulatory	10 (19)	7 (18)	6 (12)	8 (21)	—	—	16 (31)	15 (38)	0.51
Metabolic	22 (42)	19 (49)	7 (13)	2 (5)	1 (2)[a]	2 (5)[a]	30 (58)	23 (59)	1.00
Dermatologic	13 (25)	2 (4)	2 (4)	0 (0)	—	—	15 (29)	2 (5)	0.006
Overall neurologic	27 (52)	8 (21)	4 (8)	1 (3)	—	—	31 (60)	9 (23)	0.0006
Sensory	9 (17)	2 (5)	2 (4)	—	—	—	11 (21)	2 (5)	0.04
Motor	17 (33)	5 (13)	1 (2)	0 (0)	—	—	18 (34)	5 (13)	0.03
Cortical	12 (23)	4 (10)	1 (2)	1 (3)	—	—	13 (25)	5 (15)	0.18
Cerebellar	3 (6)	—	—	—	—	—	3 (6)	0(0)	0.25

[a] Tumor lysis.

TABLE 5
Best Response and Outcome by Treatment Cohort

	No. of patients (%)		
Response[a]	Cohort 1 (n = 52)	Cohort 2 (n = 40)	*P* value
CR	41 (79)	27 (68)	NS
PR	5 (10)	5 (12)	NS
PD	4 (8)	3 (8)	NS
Overall response	46 (89)	32 (80)	NS
Early death	2 (4)	5 (12)	NS
CNS recurrence	2 (4)	2 (5)	NS

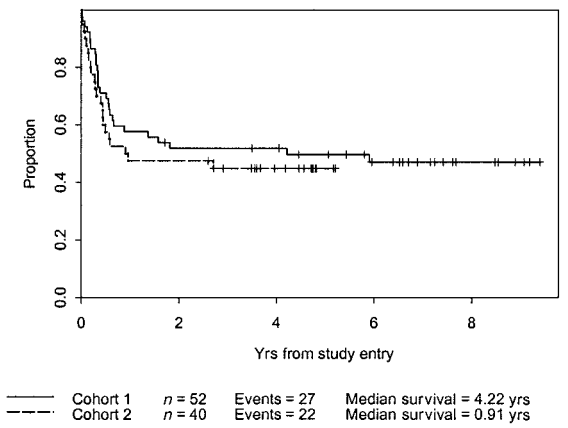
CR: complete response; NS: not significant; PR: partial response; PD: progressive disease; CNS: central nervous system.

[a] Response was evaluated first at the end of Cycle 2 and every 2 cycles thereafter.

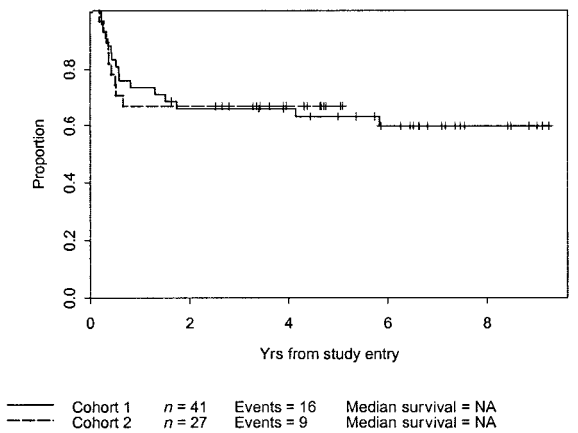
Cohort 2. The DFS rates were 66% (95% CI, 51–80%) and 67% (95% CI, 49–84%) for Cohort 1 and Cohort 2, respectively; and the OS rates were 54% (95% CI, 40–67%) and 50% (95% CI, 35–65%) for Cohort 1 and Cohort 2, respectively. There were only 2 events after 3 years of follow-up in Cohort 1 (both recurrences) and 1 event after 3 years in Cohort 2 (1 patient with a long partial response received high-dose therapy and underwent bone marrow transplantation 2.7 years after initial therapy). The outcomes for patients with Burkitt lymphoma and leukemia were similar. The outcomes of all 133 patients enrolled on the study were similar to the outcomes for the 92 patients with Burkitt leukemia/lymphoma, as presented here in detail (data not shown).

Among the subgroup of 26 patients who had a confirmed t(8;14) or typical variant, 4 patients had lymphoma, whereas the remaining 22 had leukemia. Twenty of those patients achieved a remission (77%; 95% CI, 56–91%). The 1-year EFS, DFS, and OS rates for these 26 patients were 54% (95% CI, 35–73%), 70% (95% CI, 50–90%), and 54% (95% CI, 35–73%), respectively. There were no events after 1 year, and patients in this group who were treated before or after the amendment to the regimen had no significant difference in any of the outcomes described above (all P values > 0.20).

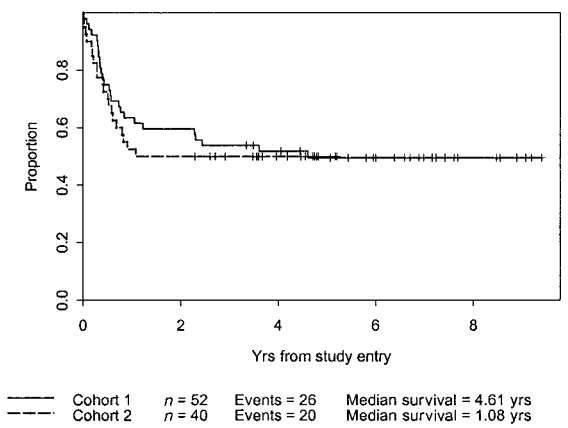
EFS by IPI risk group for all eligible patients is shown in Figure 2. Significantly better response, EFS, and OS were observed in the low-risk and low-intermediate-risk groups compared with the high-risk and high-intermediate-risk groups (likelihood ratio chi-square test; $P = 0.002$). Regression analysis revealed that age was the most important factor in predicting the likelihood of remission, whereas performance status at diagnosis was related significantly to EFS, DFS, and OS. There were no differences in response rate, DFS, or OS when either low-risk or high-risk patients were compared before and after the amendment that reduced CNS prophylaxis; however, the subgroups for this analysis were small, and thus they are not presented separately.



A



B



C

FIGURE 1. (A) Event-free survival by treatment cohort. Chi-square = 0.52; $P = 0.471$. (B) Disease-free survival by treatment cohort. Chi-square = 0.0037; $P = 0.9515$. (C) Overall survival by treatment cohort. Chi-square = 0.15; $P = 0.699$. NA: not available.

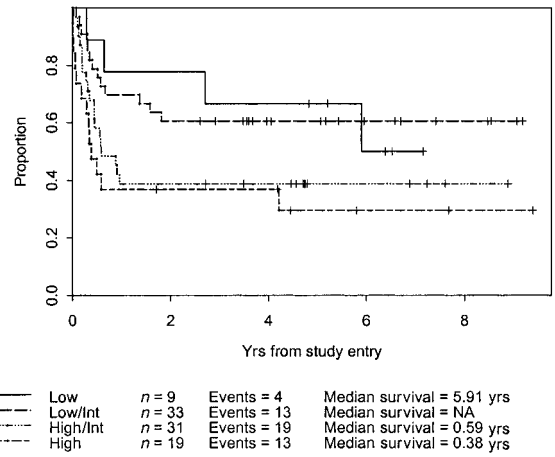


FIGURE 2. Overall survival with 95% confidence intervals (95% CIs) at 3 years by International Prognostic Index score. Overall survival: low, 0.78 (95% CI, 0.51–1.00); low-intermediate (Low/Int), 0.67 (95% CI, 0.50–0.83); high-intermediate (High/Int), 0.39 (95% CI, 0.22–0.56); high, 0.37 (95% CI, 0.15–0.59). Chi-square = 7.96; $P = 0.047$. NA: not available.

DISCUSSION

Burkitt lymphoma and leukemia form a continuum in terms of an uncommon disease with increasing involvement of the bone marrow and blood. Patients with such malignancies share a high proliferative rate and similar morphology, immunophenotype, cytogenetics, and response rates. Thus, it is appropriate to evaluate the efficacy and toxicity observed when these patients are enrolled on a uniform treatment protocol.

Therapy with standard multiagent chemotherapy commonly used for other types of lymphoma or ALL has failed to yield significant long-term survival in adults with Burkitt leukemia/lymphoma.[16] Intensive, multiagent schemes that include antimetabolites, such as methotrexate (MTX) and cytarabine, when used to treat younger patients, have led to response rates near 80% and encouraging DFS rates ($> 40\%$).[5,11–14,16] The approach evaluated in the current protocol is similar to what has been reported by the German Multicenter ALL Study Group[7] and by Magrath et al.[17] and Adde et al.[18] Furthermore, although cranial radiation is often used in the treatment of patients with precursor-B acute leukemia, its role in patients with Burkitt leukemia is questionable, particularly in regimens that incorporate high-dose MTX.[19] It is noteworthy that the current trial added to the findings of these previous studies with a longer median follow-up duration and focused evaluation of older adult patients (median age, 47 years, with no upper cutoff age). Table 6 shows that recent studies have not included prophylactic cranial radiotherapy in the treatment of patients with Burkitt leukemia/lym-

TABLE 6
Comparison of the Current Regimen of Central Nervous System Prophylaxis with Other Reported Regimens Combining High-Dose Alkylators and Methotrexate-Intensive Therapy

Variable	Mead et al., 2002[15] (CODOX-M/IVAC)	Magrath et al., 1996[17] (CODOX-M/IVAC)	Hoelzer et al., 1996[7] (GMALL trials)	Soussain et al., 1995[6] (LMB trial)	Thomas et al., 1999[23] (Hyper-CVAD-Ara-C/MTX)	Current study	
						Cohort 1	Cohort 2
No. of patients	52	72	68	65	21	52	40
Age range (yrs)	Various ages	2–59	15–65	17–65	≥ 17	> 17	> 17
Systemic MTX dose (no. of cycles)	1.44 g (2–3)	A) 2.76 g (6); B) 1.44 g (2)	A) Induction 20 mg/m^2 weekly for 2 yrs; B) 500 mg/m^2 (6); C) 1.5 g/m^2 (6)	A) 3 g/m^2; B) 8 g/m^2	1 m/m^2 (4)	1.5 gm/m^2 (7)	1.5 g/m^2 (7)
Systemic Ara-C dose (no. of cycles)	8 g/m^2 (2) (in high-risk patients only)	8 g/m^2 (2) (in high-risk patients only)	A) 450 mg/m^2; B) 300 mg/m^2; C) 450 mg/m^2 (3)	A) 500 mg/m^2; B) 12 g/m^2	12 g/m^2 (4)	300 mg/m^2 (3)	300 mg/m^2 (3)
IT-MTX dose (no. of cycles)	12 mg (4)	12 mg (6; 4 if high risk)	10–15 mg/m^2 (4–6)	8–10 doses	12 mg (8)	15 mg (12)	15 mg (6)
IT-Ara-C dose (no. of cycles)	70 mg (3)	70 mg (12; 3 if high risk)	40 mg (6 [some patients])	8–10 doses	100 mg (8)	40 mg (12)	40 mg (6)
IT-HC dose (no. of cycles)	None	None	4 mg dexamethasone (6 [some patients])	8–10 doses	None	50 mg (12)	50 mg (6)
Cranial RT	None	If high risk	2400–3000 cGy to 38/52 (72%)	Variable	None	2400 cGy	2400 cGy (only for high-risk patients)
Modifications	—	Removed 1 dose of Vcr per cycle	—	MTX/Ara-C reduced in older adults	MTX/Ara-C reduced in 76% of patients	—	—
Severe neurologic toxicity	3% Grade 3 in high-risk group, but other toxicity not reviewed in detail	Sensory in 6/12 before modification; 27% sensory, 27% motor, 5% seizures in high-risk group	One cortical, but other toxicity not reported in detail; RT related to delayed neutrophil recovery and mucositis	One cerebellar, but other toxicity not reviewed in detail	Four of 21 (19%) Grade 3–5; 3 cerebellar, 1 DI	Three transverse myelitis; 2 peripheral neuropathy; 3 aphasia; 1 blindness	Five motor weakness; 1 seizure
CNS recurrence (%)	0 (0)	0 (0)	0 (0)	Not reported	Not reported	2 (4)	2 (5)

CODOX-M/IVAC: cyclophosphamide, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and high-dose cytarabine; GMALL: German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (ALL); MB: protocol for B-cell non-Hodgkin lymphoma and B-ALL; Hyper-CVAD: fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone; Ara-C: cytosine arabinoside; MTX: methotrexate; IT: intrathecal; HC: hydrocortisone; RT: radiation therapy; |cGy: centigrays; Vcr: vincristine; DI: diabetes insipidus; CNS: central nervous system.

phoma, except for those with *high-risk* disease. Nineteen of 92 patients (21%) were age > 60 years, with the eldest patient age 78 years. Although this regimen is difficult, patients age > 60 years who attained a remission had leukemia-free survival that was similar to that of younger patients who experienced remission. Using the IPI criteria, over half of the patients in the current study were at high-intermediate or high risk. Seventy-nine percent had Stage IV disease due to bone marrow involvement, another important point when comparing these outcomes with previous reports involving younger and often lower-risk patients. Plateaus were noted on the Kaplan–Meier curves for DFS at 65–70% and on the curves for EFS at approximately 50%, with very few recurrences after 1 year. Our high response rates, DFS, and EFS in this patient population remain encouraging. However, after stratifying patients by IPI criteria, it is clear that those with high-risk or high-intermediate-risk disease had poorer outcomes; thus, the pursuit of different experimental approaches for this group is particularly worthwhile.

Pancytopenia was encountered in all patients, as anticipated, and many patients had febrile neutropenia. Infections and gastrointestinal side effects were the next most common toxicities, with the majority of patients noting severe stomatitis or esophagitis, although the second cohort had significantly fewer gastrointestinal side effects overall. Newer ancillary agents for decreasing integument damage also may yield reduced gastrointestinal toxicity and better tolerance for this therapy. Agents such as keratinocyte growth factors, oral thiol-containing compounds, and oral prophylactic antibiotics currently are under evaluation.[21,22] The use of hematopoietic growth factors for this purpose has met with mixed success to date, although some studies suggest that granulocyte–colony-stimulating factor may improve outcomes.[23] It is particularly important to improve the tolerance of remission induction treatment in older patients, because the DFS of patients age > 60 years was equivalent to the DFS of younger patients in the current trial.

In an attempt to improve the tolerance of the previously reported intensive, short-duration approaches, the current study allowed a comparison to be made between similar groups of patients who differed only in terms of the CNS prophylaxis that was received. The degree of severe neurologic toxicity in the first cohort was not encountered in the second cohort of patients, whereas outcomes were equivalent in the preamendment and postamendment groups in terms of response rate, DFS, EFS, and OS. The difference in neurotoxicity is particularly striking when comparing only those in the low-risk group preamendment and postamendment. Low-risk patients in Cohort 2 tolerated the protocol with only 9% severe neurotoxicity, compared with a 62% rate of severe neurotoxicity in similar patients in Cohort 1. The current study confirmed the results of previous studies primarily involving younger patients and revealed that high-dose antimetabolites and intrathecal therapy can effectively reduce CNS recurrences in this potential reservoir site and can make the overall chemotherapy regimen more tolerable. Thus, cranial radiation can be reserved for patients who have proven CNS involvement.

Previous reports focused primarily on treating younger patients and noted variability in the methods used to prevent CNS recurrence. The doses, sequence, and timing in relation to systemic therapy differed among studies and often within each study, making direct comparisons of risks and benefits specific to CNS prophylaxis difficult. The current study provides a direct comparison of sequential cohorts of adult patients who were treated in an identical manner except for the CNS therapy received. The doses of systemic MTX and cytarabine used in the current study were similar to those used in some patient subgroups in many of the LMB trials but were greater than doses used in other subgroups in these trials[6,24] and in the more recent report by Hoelzer et al.[7] However, the doses we used are lower than the high-dose MTX and cytarabine doses used in the recent Berlin–Frankfurt–Munster Group trials, although those trials focused on treatment of patients age < 18 years.[25] The systemic MTX dose used in the current study was similar to the doses used in the fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone (hyper-CVAD)-cytosine arabinoside (ara-C)/MTX (hyper-CVAD-ara-C/MTX)[23] and cyclophosphamide, doxorubicin, and high-dose MTX (CODOX-M) alternating with ifosfamide, etoposide, and high-dose cytarabine (IVAC) (CODOX-M/IVAC)[15,17] combinations referenced here. However, these regimens involved high doses of systemic cytarabine. Intrathecal therapy and cranial radiation in the first cohort of patients was aggressive. It is noteworthy that the hyper-CVAD-ara-C/MTX and CODOX-M/IVAC combinations have demonstrated the safety of eliminating the use of prophylactic cranial radiation in favor of more intensive intrathecal and systemic chemotherapy (as noted above). The protocol followed for the second cohort, with half the number of intrathecal injections and the use of cranial radiation only in high-risk patients, delivered less intensive therapy overall to the CNS compared with the other trials cited above.

Neurotoxicity remains a concern when each of the prior regimens is used in adults.[15,17,23] The neurotox-

icities commonly observed in the current study included those that are well recognized by oncologists: peripheral neuropathy due to vincristine, myopathy due to steroids, and cortical toxicity due to high-dose MTX. In large part, these toxicities were reversible. Even without common usage of cranial radiation, summaries of reported toxicities with the hyper-CVAD-ara-C/MTX and CODOX-M/IVAC combinations referenced here (Table 6) indicate significant neurotoxicity (in the 20% range), with sensory, motor, cortical, and cerebellar toxicity all reported. Severe cortical and cerebellar toxicity was noted in some patients who were treated using the GMALL and LMB regimens, although the degree of neurotoxicity in adults is not reported in detail. The first cohort of patients experienced severe toxicity, similar to what was observed in the reports cited in Table 6. However, in Cohort 2, in which less intensive CNS prophylaxis was used, there was only one patient with therapy-related seizures, along with a small number of patients with transient weakness. Overall, significantly less neurologic toxicity in this group of adult patients was noted, and there were no episodes of myelitis, blindness, cortical atrophy, aphasia, or cerebellar toxicity. The success noted in the second cohort in the current study has led to our current CALGB trial, in which we have eliminated prophylaxis involving cranial radiation altogether and in which we rely solely on the use of high-dose antimetabolites and the less intensive intrathecal triple therapy. Prophylactic cranial radiotherapy will not be administered to patients with normal CSF.

Further progress in the treatment of patients with this disease may be made by combining multiagent chemotherapy with newer modalities, such as monoclonal antibodies. The CD20 antigen is expressed at high levels in $>$ 90% of patients with Burkitt leukemia or lymphoma, suggesting a potential role for rituximab.[26,27] The CALGB recently activated a Phase II trial evaluating this chemotherapy regimen plus rituximab and granulocyte–colony-stimulating factor for newly diagnosed patients.

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