Chemoimmunotherapy with Hyper-CVAD plus Rituximab for the Treatment of Adult Burkitt and Burkitt-Type Lymphoma or Acute Lymphoblastic Leukemia

Deborah A. Thomas, M.D.[1]
Stefan Faderl, M.D.[1]
Susan O'Brien, M.D.[1]
Carlos Bueso-Ramos, M.D., Ph.D.[2]
Jorge Cortes, M.D.[1]
Guillermo Garcia-Manero, M.D.[1]
Francis J. Giles, M.D.[1]
Srdan Verstovsek, M.D., Ph.D.[1]
William G. Wierda, M.D., Ph.D.[1]
Sherry A. Pierce, B.S.N.
Jianqin Shan, Ph.D.[1]
Mark Brandt[1]
Fredrick B. Hagemeister, M.D.[3]
Michael J. Keating, M.B., B.S.[1]
Fernando Cabanillas, M.D.[3]
Hagop Kantarjian, M.D.[1]

[1] Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[2] Department of Hematopathology, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[3] Lymphoma and Myeloma Center, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Address for reprints: Hagop Kantarjian, M.D., Department of Leukemia, Unit 428, University of Texas M. D. Anderson Cancer Center, P.O. Box 301402, Houston, TX 77230-1402; Fax: (713) 794-4297; E-mail: hkantarj@mdanderson.org

Received June 23, 2005, revision received October 2, 2005; accepted November 2, 2005.

BACKGROUND. Adult Burkitt-type lymphoma (BL) and acute lymphoblastic leukemia (B-ALL) are rare entities composing 1% to 5% of non-Hodgkin lymphomas NHL) or ALL. Prognosis of BL and B-ALL has been poor with conventional NHL or ALL regimens, but has improved with dose-intensive regimens.

METHODS. To evaluate the addition of rituximab, a CD20 monoclonal antibody, to intensive chemotherapy in adults with BL or B-ALL, 31 patients with newly diagnosed BL or B-ALL received the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen with rituximab. Their median age was 46 years; 29% were 60 years or older. Rituximab 375 mg/m^2 was given on Days 1 and 11 of hyper-CVAD courses and on Days 1 and 8 of methotrexate and cytarabine courses.

RESULTS. Complete remission (complete response [CR]) was achieved in 24 of 28 (86%) evaluable patients; 3 had a partial response, and 1 had resistant disease. There were no induction deaths. The 3-year overall survival (OS), event-free survival, and disease-free survival rates were 89%, 80%, and 88%, respectively. Nine elderly patients achieved CR with all of them in continuous CR (except 1 death in CR from infection), with a 3-year OS rate of 89%. Multivariate analysis of current and historical (those treated with hyper-CVAD alone) groups identified age and treatment with rituximab as favorable factors.

CONCLUSIONS. The addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL, particularly in elderly patients. ***Cancer*** **2006;106:1569–80.**

KEYWORDS: adult Burkitt lymphoma, BL, acute lymphoblastic leukemia, B-ALL, chemoimmunotherapy, hyper-CVAD, rituximab.

Adult Burkitt-type lymphoma (BL) and acute lymphoblastic leukemia (B-ALL) are rare entities accounting for 1% to 5% of non-Hodgkin lymphomas (NHL) or ALL.[1,2] BL and B-ALL are composed of high-grade rapidly proliferating small noncleaved mature B lymphoid cells with propensity for central nervous system (CNS) involvement. B-ALL is characterized by L3 morphology according to the French–American–British classification,[3] mature B-cell immunophenotype with surface immunoglobulins (sIgs), and translocations involving chromosome 8 [t8;14(q24;q32); t(2;8)(p12;q24), and t(8;22)(q24;q11)]. These translocations [with immunoglobulin (Ig) heavy-chain gene locus on 14q32 in t(8;14); Ig kappa on 2p12 in t(2;8); or Ig lambda on 22q11 in t(8;22)] lead to inappropriate expression of the proto-oncogene c-*myc* on band 8q24.[4] Some B-ALL cases exhibit morphology of

DOI 10.1002/cncr.21776
Published online 24 February 2006 in Wiley InterScience (www.interscience.wiley.com).

TABLE 1
Short-Term Dose-Intensive Regimens in Adult BL and B-ALL

Study	Therapy	No. Pts	Age		% CR	% CR (X yrs)	% Survival (X yrs)
			Median	% ≥ 60 y			
Hoelzer[16]	B-NHL83	24	33	0	63	50 (8)	49 (8)
	B-NHL86	35	36	≈ 10	74	71 (4)	51 (4)
Hoelzer[23]	B-NHL90	45	NR	All > 55	71	NR	39 (6)
Magrath[10]	89-C-41 (CODOX-M/IVAC)	20	25	0	89	89 (2)	74 (4)
Soussain[18]	LMB 81, 84, 86, 89	65	26	≈ 2	89	NR	72 (3)
		22	NR	0	77	NR	57 (3)
Mead[21]	CODOX-M/IMVAC	52	35	NR*	75	NR	73 (2)
Rizzieri[20]	CALGB 9251						
	Cohort 1	52	44	19	79	66 (3)	54 (3)
	Cohort 2	40	50	23	68	67 (3)	50 (3)
Di Nicola[22]	CMVP-16/Ara-C/CDDP	22	36	NR†	77	68 (2)	77 (2)
Thomas[17]	Hyper-CVAD	26	58	46	81	61 (3)	49 (3)
	Age < 60	14	38	—	93	83 (3)	77 (3)
	≥ 60	12	NR	—	—	—	17 (3)
Current	Hyper-CVAD	48	48	33	85	60 (3)	53 (3)
	Hyper-CVAD + rituximab	31	46	29	86	88 (3)	89 (3)

BL: Burkitt lymphoma; B-ALL: Burkitt-type acute lymphoblastic leukemia; CR: complete remission; X yrs: year reported; NR: not reported; CODOX-M/IMVAC: cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine; CDDP: cisplatin; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine.

* None older than 60 years.

† 31% aged ≥ 50.

L1 or L2 lymphoblasts with sIg expression and typical Burkitt karyotype.[2] Coexpression of t(14;18)(q32;q21) (with aberrant expression of antiapoptotic bcl-2) with a Burkitt translocation may confer worse prognosis.[5] Increased frequency of t(14;18) in older adults with B-ALL may account for some of the age-related differences in outcome.[6]

Prognosis of BL and B-ALL was poor with conventional NHL or ALL regimens. Complete response (CR) rates ranged from 30% to 70% with cure rates 0% to 30%.[7–10] High growth fractions favored reentry of viable cells into the cell cycle with rapid regrowth between chemotherapy courses. Improvements in outcome were not observed until short-term dose-intensive multiagent chemotherapy regimens incorporating fractionated cyclophosphamide, high-dose methotrexate (MTX), and cytarabine (cytosine arabinoside [ara-C]) were used. In children, CR rates improved to 90% or better with cure rates 50% to 90%[11-15]; for adults CR rates were 60% to 80% and cure rates 40% to 60%.[16–22]

In most adult series of BL and B-ALL, median age is 25 to 30 years. In a prior study of the intensive hyper-CVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) for B-ALL at our institution, median age was 58 years, and outcome was age-dependent.[17] Patients younger than 60 years had a CR rate of 90% with cure rate of 70%, whereas older patients had a CR rate of 67% with cure rate of only 15%. Similar age-associated prognostic differences were noted in German studies of B-ALL[16,23] and BL.[24] CR rate was 71% with 6-year survival rate 39% among 45 elderly (age > 55 yrs) patients who received intensive chemotherapy (protocol B-NHL90). Identification of age as a major prognostic factor has further highlighted the need to compare different treatment programs within similar age-defined prognostic groups and emphasizes the need to develop more effective (yet not more toxic) therapy for BL and B-ALL (Table 1).[10,16–18,20–23]

Rituximab, a CD20-directed monoclonal antibody, has activity in several lymphoid malignancies, including indolent and aggressive NHL[25] and chronic lymphocytic leukemia (CLL).[26,27] A combined chemoimmunotherapy regimen with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab in elderly patients with aggressive NHL improved prognosis significantly compared with CHOP alone, without additional toxicity.[28] Because BL and B-ALL are characterized by strong surface expression of CD20, rituximab was incorporated into hyper-CVAD[17] in a Phase II clinical trial. Herein, we summarize results of the hyper-CVAD plus rituximab regimen and update the experience with hyper-CVAD[17] in adult BL and B-ALL.

MATERIALS AND METHODS

Study Group

Thirty-one consecutive adults with newly diagnosed BL and B-ALL who were referred to M. D. Anderson Cancer Center, either untreated ($n = 27$) or after 1 course of chemotherapy ($n = 4$), received hyper-CVAD plus rituximab between February 2000 and January 2005. Informed consent was obtained according to institutional guidelines after approval by the Institutional Review Board. Eligibility criteria included age ≥ 15 years and ECOG performance status 3 or better with no restrictions for older age, organ dysfunction, or presence of human immunodeficiency virus (HIV). Ten patients with HIV-related BL will be reported separately.[29] Documented diagnosis of BL or B-ALL (latter with ≥ 25% marrow blasts or $\geq 10 \times 10^9$/L peripheral blasts) was required as confirmed by enzymatic stains. Burkitt or Burkitt-like subtypes were identified by 1) BL morphology with high Ki-67 expression or L3 morphology or by 2) L1 or L2 morphology with Burkitt karyotype or mature B-cell immunophenotype (sIg positivity ≥ 20% or κ/λ light-chain clonality with B-lineage antigens CD19 or CD20) and c-*myc* rearrangement by fluorescent in situ hybridization or Southern blot analysis.

Pretreatment evaluations included history with physical examination and documentation of extramedullary disease (EMD) by imaging and/or appropriate cytologic/histologic evaluations; complete blood count with differential; hepatic and renal function studies with lactate dehydrogenase (LDH) and uric acid levels; and bone marrow aspirate/biopsy for morphology, immunohistochemical stains, immunophenotyping, and karyotyping. Analysis of cerebrospinal fluid (CSF) was performed concomitantly with prophylactic intrathecal (IT) treatment approximately Day 2 of chemotherapy. Abnormal chest radiographs were evaluated further by imaging with computed tomography (CT). Magnetic resonance imaging (MRI) and/or CT of the brain was performed for cranial nerve palsies or positive CSF cytology. Abnormal radiographic studies were repeated to document CR. Baseline marrow aspirations were repeated on Days 14 and 21 of Course 1 if involved (or later to confirm CR if needed), then every 2 to 3 courses until end of therapy, then every 3 to 6 months for the first 2 years.

Therapy

Chemotherapy consisted of 8 alternating courses every 21 days, or earlier if count recovery occurred (at least 14 days apart), without maintenance therapy.[17] Rituximab was given during Courses 1 to 4. Odd courses (1,3,5,7) were hyper-CVAD 1) hyper-fractionated cyclophosphamide 300 mg/m^2 intravenously (i.v.) every 12 hours for 6 doses Days 1 to 3 with sodium mercaptoethanesulfonate 600 mg/m^2 daily via continuous infusion Days 1-3; 2) vincristine 2 mg i.v. Days 4 and 11; doxorubicin 50 mg/m^2 i.v. over 24 hours via central venous catheter Day 4; and dexamethasone 40 mg daily Days 1 to 4 and 11 to 14. To prevent tumor lysis syndrome (TLS), Course 1 included i.v. hydration with alkalinization and allopurinol (or urate oxidase for high tumor burden). Oral sodium bicarbonate was also given Days 1 to 3. Even courses (2,4,6,8) were MTX and ara-C as follows: MTX 1 g/m^2 i.v. over 24 hours Day 1 and ara-C 3 g/m^2 i.v. every 12 hours for 4 doses Days 2 and 3 (once serum MTX level at end of infusion [0 hour] reached ≤ 20 μmol/L). Intravenous alkalinization was used to promote excretion of MTX in all courses. Calcium leucovorin 50 mg i.v. was given 12 hours after completion of MTX, then 15 mg i.v. every 6 hours for 8 doses or until MTX levels were < 0.1 μmol/L. An algorithm of additional leucovorin rescue (50-100 mg i.v. every 4-6 hours) was implemented if MTX levels were elevated (0 hour [repeated if elevated] ≥ 20 μmol/L, 24 hour ≥ 1 μmol/L, 48 hour > 0.1 μmol/L). Oral acetazolamide was given for urine pH < 7.0.

Rituximab was given 375 mg/m^2 i.v. over 2 to 6 hours on Days 1 and 11 of hyper-CVAD and on Days 2 and 8 of MTX and ara-C, was given for 8 doses over the first 4 courses.

Standard dose reductions included 1) ara-C 1 g/m^2 for age ≥ 60 years, creatinine ≥1.5 mg/dL or 0 hour MTX level ≥ 20 μmol/L; 2) vincristine 1 mg for bilirubin > 2 mg/dL or NCI common toxicity criteria Grade 2+ peripheral neuropathy (eliminated for bilirubin > 3 mg/dL or for ileus); 3) doxorubicin by 50% for bilirubin 2 to 3 mg/dL, by 75% for bilirubin 3 to 5 mg/dL (eliminated for bilirubin > 5 mg/dL or for gastric/small-bowel involvement with Course 1 to reduce duration of myelosuppression given risk of perforation); and 4) MTX by 50% for creatinine clearance 10 to 50 mL/min (eliminated for < 10 mL/min), by 25% to 75% for delayed excretion and/or nephrotoxicity with prior course (dependent on severity) or by 50% for pleural effusions/ascites with drainage of fluid as feasible.

Granulocyte colony-stimulating factor (G-CSF) 10 μg/kg subcutaneously daily started 24 hours after chemotherapy completion and continued until white blood cell count (WBC) reached ≥ 3×10^9/L unless bone pain was present. To maintain dose intensity, subsequent courses were initiated when the unmaintained WBC count was ≥ 3×10^9/L and the platelet count (PLT) was ≥ 50×10^9/L. If WBC was ≥ 3×10^9/L but PLT was < 50×10^9/L, G-CSF was discontinued

with reassessments every 3 to 5 days until platelet recovery.

CNS prophylaxis alternated IT MTX 12 mg (6 mg by Ommaya reservoir) on Day 2 and ara-C 100 mg on Day 7 of each course (16 IT treatments).[17] If there was CNS involvement, IT therapy was augmented to twice weekly until CSF cell count normalized and cytology was negative for malignant cells. The IT therapy then alternated MTX and ara-C weekly for 4 doses (including planned IT Days 2 and 7 if course given). The program was then resumed for prophylaxis until completion of chemotherapy. No prophylactic cranial irradiation (XRT) was administered. Therapeutic XRT was given if indicated, e.g., for cranial nerve palsies or intracranial mass (separaed from intrathecal or systemic methotrexate by at least 2 weeks).

Supportive Care

Patients aged 60 years or older were placed in a laminar air-flow room or protective environment (PE) for Course 1 until absolute neutrophil count (ANC) reached 0.5×10^9/L. All patients received oral prophylactic antibiotics (e.g., quinolone or trimethoprim-sulfamethoxazole; fluconazole; and valacyclovir or acyclovir). Hematologic profiles were obtained at least biweekly during induction and at least weekly during consolidations. Packed red blood cells were given for symptomatic and/or severe anemia with platelet transfusions for platelets ≤ 10 to 15×10^9/L or if $\leq 50 \times 10^9$/L with hemorrhage. Neutropenic febrile episodes generally resulted in patient hospitalization for administration of broad-spectrum parenteral antibiotics.

Response Criteria

Response criteria were as previously reported for B-ALL.[17] For BL, CR required complete disappearance of all known disease. Partial response (PR) was defined as $\geq 50\%$ reduction in tumor size. Progressive disease (PD) included new lesions or a 25% increase in size of existing lesions. Other response outcomes were induction death if death occurred after start of therapy without reaching CR or resistant disease (surviving treatment period but failing to respond) definitions. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (version 2.0).

Comparison with Hyper-CVAD alone

Results of hyper-CVAD plus rituximab were compared with our historical experience with hyper-CVAD (initially reported on 26 patients[17]), updated for purposes of the comparative analysis. From September 1992 to January 2000, 48 consecutive patients received hyper-CVAD, and from February 2000 to January 2005, 31 patients received hyper-CVAD plus rituximab. There were no planned differences in chemotherapy or supportive care other than addition of rituximab and use of PE for Course 1; the latter was implemented because of an infection-related induction mortality rate of 33% in the elderly ($\geq$ 60 yrs).[17]

Characteristics of the 2 consecutive study groups are detailed in Table 2. The median age of the historical group was 48 years; 16 (33%) were aged 60 years or older. Although differences in performance status were noted, other factors (e.g., anemia, thrombocytopenia, circulating blasts, or hepatomegaly) were related to the lower proportion of B-ALL in the study cohort compared with the historical group. Conversely, the higher proportion of extramedullary disease (EMD) in the study cohort reflected predominance of BL presentation. In comparing elderly patients treated with hyper-CVAD plus rituximab ($n = 9$) vs. hyper-CVAD ($n = 16$) with respect to parameters in Table 2, the only differences observed were in frequency of adenopathy (57% vs. 13%, respectively, $P = .02$) and thrombocytopenia (22% vs. 81%, respectively, $P = .007$; data not shown). Because these were consecutively treated patients, the differences likely reflected heterogeneity in disease presentations over the 13-year period. Multivariate analysis (MVA) was used to account for these differing variables in analyzing determinants of outcome.

Statistical Methods

Survival was measured from initiation of therapy until death. Disease-free survival (DFS) was measured from CR until relapse or death. Event-free survival (EFS) was measured from start of therapy until failure to respond, or until relapse or death. CR duration (CRD) was measured from CR until relapse. A cutoff date of March 21, 2005 was established for analyzing data for this report. Unadjusted survival, CRD, and DFS analyses were performed by using Kaplan–Meier plots[30] with differences among them analyzed by the log-rank test.[31] Goodness-of-fit was assessed by martingale residual plots.[32] The Cox proportional hazards model[33] was used to assess treatment and patient characteristics in predicting survival, CRD, and DFS. Factors significant for survival or CRD/DFS outcomes by univariate analysis were analyzed further by stepwise regression by using the assumption of proportional hazards suggested by Cox.[33]

RESULTS

Study Group

The median age of the study group was 46 years (range, 17-77 yrs; median for $<$ 60 yrs was 39 yrs); 29% were $\geq$ 60 years (Table 2). Four responders had 1 prior

TABLE 2
Characteristics of Study and Historical Groups

Characteristic	Hyper-CVAD + Rituximab no. (%)	Hyper-CVAD Alone no. (%)	*P*
Total	31	48	—
Female gender	7 (23)	10 (21)	NS
ECOG performance status 3-4	0 (0)	8 (17)	.02
Age, y			NS
≥ 60	9 (29)	16 (33)	—
Overall median (range)	46 (17-77)	48 (16-79)	—
Disease state			<.01
BL*	17 (55)	7 (15)	—
B-ALL	14 (45)	41 (85)	—
Morphology			<.01
Burkitt	15 (48)	44 (92)	—
Burkitt-like	16 (52)	4 (8)	—
Karyotype			.10
t(8;14), t(2;8) or t(8;22)	11 (36)	15 (31)	—
t(14;18) or 14q32 only	1 (3)	4 (8)	—
Diploid, hyper, or pseudo	16 (52)	15 (31)	—
Insufficient metaphases or not available	3 (10)	14 (29)	—
WBC ≥ 10×10^9/L	13 (42)	14 (29)	NS
Hemoglobin < 10 g/dL	9 (29)	30 (62)	<.01
PLT < 100×10^9/L	9 (29)	31 (65)	<.01
Peripheral blasts present	10 (32)	29 (60)	.01
% Bone marrow blasts			.01
25-49	1 (3)	4 (9)	—
≥ 50	13 (42)	31 (70)	—
Lactate dehydrogenase, U/L (ULN 618)			.09
620-4999	13 (43)	25 (52)	—
5000-10,000	3 (10)	9 (19)	—
> 10,000	5 (17)	10 (21)	—
Albumin < 3 g/dL	8 (27)	14 (29)	NS
B_2 microglobulin ≥ 3 mg/dL	15/25 (60)	24/41 (59)	NS
Bilirubin ≥ 1.0 mg/dL	5 (17)	14 (30)	NS
Creatinine ≥ 1.5 mg/dL	5 (17)	3 (6)	NS
Hepatomegaly	2 (7)	11 (23)	.05
Splenomegaly	4 (13)	13 (27)	NS
Peripheral adenopathy	11 (35)	12 (25)	NS
CNS leukemia	2 (7)	10 (21)	0.08
Extramedullary disease other than CNS	18 (58)	8 (17)	<.01
Gastrointestinal disease	13 (42)	6 (12)	<.01

ECOG: Eastern Cooperative Oncology Group; BL: Burkitt lymphoma; B-ALL: Burkitt-type acute lymphoblastic leukemia; CNS: central nervous system; ULN: upper limit normal.
* Ki-67 expression > 90% in all cases.

course of chemotherapy. Three had hyper-CVAD plus rituximab and started with Course 2 of high-dose MTX, ara-C, and rituximab as allowed for logistical reasons ($n = 2$) or outside therapy. One had CHOP plus rituximab with residual bulky disease. These patients were included in the analysis (there was no difference in outcome by inclusion or exclusion of these 4 patients.). Three patients entered study with resected disease and, therefore, were not evaluable for response. Cytogenetics showed characteristic translocations in 11 of 14 (79%) B-ALL patients with t(8;22) t(14;18)(q32;q31) in 2 patients (aged 72 and 50 yrs, respectively, the latter the only patient with resistant disease). Twenty (65%) patients had EMD, some at multiple sites as follows: 2 CNS or leptomeningeal disease; 13 gastrointestinal; 3 mediastinal/thoracic; 3 head/neck adenopathy; and 5 other (thyroid 2, liver 1, kidneys 1, testicles 1).

Response

Twenty-four of 28 (86%) evaluable patients achieved CR; 3 had PR and 1 had resistant disease (died after 3 mos with PD despite salvage therapy). There were no induction deaths. All 3 patients who achieved PR were still alive at the time of this report. Patient 1 had a large mesenteric mass without CNS or marrow in-

volvement and achieved PR after 8 courses with persistent disease by CT and positron emission tomography (PET) scans. Surgical resection of an 8 × 7 × 4 cm fibrotic mass showed viable BL. Four additional courses of hyper-CVAD plus rituximab were followed by HLA-identical sibling allogeneic stem cell transplantation (SCT) in CR. The patient remained alive without disease 15+ months from start of therapy (8+ mos from resection). Patient 2 with BL (no CNS or marrow disease) achieved PR after 5 cycles (discontinued for persistent thrombopenia) with PD at 8 mos from start of therapy and was alive at 11+ months with ongoing salvage chemotherapy. Patient 3 with B-ALL was classified as PR after 8 courses because of persistent bone radiographic abnormalities (with negative PET scan), despite resolution of all other sites of disease, and remained alive at 11+ months.

All 14 patients with marrow involvement achieved marrow CR and hematologic recovery after Course 1 of hyper-CVAD plus rituximab. Among 24 patients who achieved CR, 11 (46%) required 2 courses or more to achieve this response, for reasons of residual disease by radiographic studies, or because imaging was not performed after recovery from Course 1. None of these 11 patients have relapsed to date.

Disease Outcome

With a median follow-up of 22 months (range, 9-65 mos), 2 of 28 (7%) patients relapsed. One 46-year-old male with B-ALL relapsed 12 months from start of therapy and achieved second CR with investigational treatment. One 29-year-old female with B-ALL relapsed 6 months into CR and died 12 months from start of therapy despite salvage therapy. One male patient aged 77 years died 4 months into CR with pneumonia and multiple organ failure related to cytomegalovirus (CMV) infection. The estimated 3-year overall survival (OS), DFS, and EFS rates were 89%, 88%, and 80%, respectively (Fig. 1). Factors associated with worse survival were B-ALL diagnosis, leukocytosis, CNS involvement, elevated LDH, elevated creatinine, and higher percentage of marrow blasts (Table 3). By MVA, none of these characteristics were independently associated with worse survival.

Comparison with Hyper-CVAD Alone

The results of hyper-CVAD plus rituximab compared with hyper-CVAD alone are shown in Table 4. CR rates were similar, with a decrease in induction mortality for the elderly group (0% vs. 31%, $P = .04$). An improvement in the 3-year estimated survival, DFS, and EFS rates were observed, particularly for the elderly. Improvement in induction mortality and survival rates were related, in part, to use of the PE. However, other

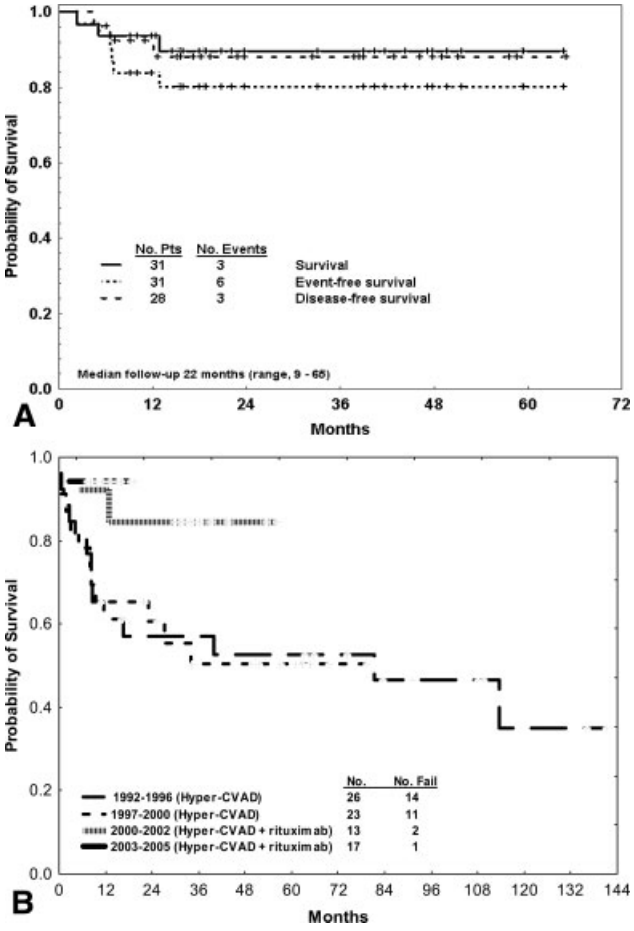

FIGURE 1. (A) Overall, event-free and disease-free survival (DFS) in BL or B-ALL after hyper-CVAD plus rituximab; (B) Survival by time period for BL or B-ALL after treatment with hyper-CVAD and rituximab or hyper-CVAD.

factors related to supportive care were unlikely to play a role in outcome, as survival remained similar around the median of the time periods of these cohorts (Fig. 1B). Reduction in the relapse rate with hyper-CVAD plus rituximab was also observed (7% vs. 34% overall, $P = .008$; 0% vs. 50% for elderly, $P = .02$; 11% vs. 29% for age < 60 yrs, $P = .11$) which translated to improved CRD and DFS rates (Figs. 2, 3).

Univariate analysis of prognostic indicators for CRD and DFS in the study and historical cohorts ($n = 69$) showed a higher risk of disease recurrence with older age, higher leukocyte counts, thrombocytopenia, higher percentage of marrow blasts, higher LDH levels, B-ALL diagnosis, adverse karyotype, higher beta-2 microglobulin levels, absence of EMD, and treatment without rituximab (Table 5). Use of the PE did not influence CRD or DFS. After accounting for these parameters, MVA identified younger age and treatment with rituximab as favorable predictors of outcome for CRD and DFS. De-

TABLE 3
Overall Survival with Hyper-CVAD Plus Rituximab by Pretreatment Characteristics

Characteristics	No. Pts	% 3-y Survival	*P* (log-rank)
Overall	31	89	
Gender			.61
Male	24	91	
Female	7	86	
Age, y			.90
< 60	22	90	
≥ 60	9	89	
ECOG performance status			.67
0-1	24	91	
2-3	7	86	
WBC (x10^9/L)			.04
< 15	24	95	
≥ 15	7	71	
Hemoglobin (g/dL)			.25
< 10	9	100	
≥ 10	22	85	
PLT (x 10^9/L)			.13
< 100	9	74	
≥ 100	22	96	
Peripheral blasts			.19
0	21	95	
≥ 1	10	77	
Lactate dehydrogenase (U/L)			.01
≤ 10,000	25	96	
> 10,000	5	53	
% Bone marrow blasts			.03
< 50	18	100	
≥ 50	13	75	
Disease state			.05
BL	17	100	
B-ALL	14	77	
Morphology			.53
Burkitt	15	85	
Burkitt-like	16	94	
CNS leukemia			<.01
Y	2	50	
N	29	92	
Gastrointestinal disease			.18
Y	13	100	
N	18	83	
B_2 microglobulin (mg/dL)			.07
< 3.5	12	100	
≥ 3.5	13	74	
Bilirubin (mg/dL)			.51
< 1.0	25	92	
≥ 1.0	5	80	
Creatinine (mg/dL)			.02
< 1.5	25	96	
≥ 1.5	5	53	

terminants of OS in the entire group (n = 79) by MVA included older age ($P < .01$), thrombocytopenia ($P = .02$), and poor performance status ($P = .04$; data not shown). After accounting for these variables, therapy with hyper-CVAD plus rituximab remained an independent favorable prognostic factor ($P<.01$; hazard ratio, 0.26).

Treatment Delivery and Toxicity

The median number of courses completed was 8; 22 of 30 (73%) patients completed all courses, and 27 of 30 (90%) at least 7 courses (1 ongoing therapy). Median time to completion was 5.5 months (range, 3.9-9.3 mos). These parameters were not significantly different from historical data.[17] Reasons for failure to complete the program were: 4 persistent thrombocytopenia without evidence of disease (after 5 courses [$n = 2$] or 7 courses [$n = 2$]); 1 poor general condition after 5 courses; 1 death in CR after 5 courses; and 1 other comorbidity.

Dose reductions of MTX and/or ara-C occurred in 17 of 30 (57%) patients; 11 (65%) had dose reductions of MTX only. Patients aged ≥60 years had ara-C reduced from 3 to 1 g/m^2 by design to avoid cerebellar neurotoxicity (none observed). Dose reductions of MTX were required in 4 of 28 (14%) patients who developed TLS during induction (all required hemodialysis with resolution of renal failure); in 7 of 30 (23%) for delayed MTX excretion and/or nephrotoxicity; in 3 (10%) for prolonged myelosuppression; and in 3 (10%) for other reasons. Hyper-CVAD courses were generally given at a 100% dosage, except for 6 (20%) patients with vincristine discontinued ($n = 2$) for ileus or severe peripheral neuropathy, or reduced dosage ($n = 4$) for patients with Grade 2+ peripheral neuropathy.

Grade 3 to 4 myelosuppression was universal and expected. Median time to ANC was 19 and 20 days at ≥1 × 10^9/L and PLT ≥100 × 10^9/L for Course 1, respectively, similar to the historical experience. With consolidation courses, median time to an ANC of ≥0.5 × 10^9/L was 15 days (range, 0-66 days) and to a PLT of ≥50 × 10^9/L was 20 days (range, 0-149 days). Thrombocytopenia-related hemorrhages (1 bladder, 1 gastrointestinal) responded to supportive care measures without sequelae.

Myelosuppression-associated infectious complications were common. Febrile episodes during Course 1 occurred in 13 of 29 (45%) patients, 5 fevers of unknown origin (FUO), 3 sepsis, 2 pneumonia, and 3 other. The incidence of febrile neutropenia for subsequent courses averaged 25% after hyper-CVAD and 40% after MTX and ara-C courses. Opportunistic infections were infrequent; 1 younger patient had respiratory synctial virus pneumonia with recovery, and 1 elderly patient died of cytomegalovirus (CMV) pneumonia with multiple organ failure.

TABLE 4
Sequential Comparison of Hyper-CVAD Plus Rituximab versus Hyper-CVAD Alone

Parameter	Hyper-CVAD Plus Rituximab (n = 31)			Hyper-CVAD Alone (n = 48)			P	
							Overall	Age ≥ 60 y
No. (%) CR	24/28* (86)			41 (85)			1.0	—
Median follow-up, mos (range)	22 (9-65)		—	74 (11-154)			—	—
Age, yrs	All	< 60	—	All	< 60	≥ 60	—	—
No. (%) induction deaths	0	0	0	6 (13)	1 (3)	5 (10)†	.04	—
% Relapse	2/28 (7)	2/19 (11)	0/9 (0)	14/41 (34)	9/31 (29)	5/10 (50)	.008	.02
% 3-y Survival	89	90	89	53	70	19	< .01	< .01
% 3-y EFS	80	76	89	52	68	19	.02	< .01
% 3-y DFS	88	88	88	60	70	30	.03	.03
% 3-y CRD	91	88	100	66	73	44	.024	.016

EFS: event-free survival; DFS: disease-free survival; CRD: complete response duration.

* Three patients were not evaluable for response and had resected disease at study start.

† Induction mortality was 31% for age ≥ 60 years.

DISCUSSION

Hyper-CVAD is an effective dose-intensive chemotherapy regimen for BL or B-ALL; however, worse outcome was noted in the elderly compared with their younger counterparts (Table 1).[17] In addition to differences in disease biology associated with older age, this may in part be because of an inability to deliver dose-intensive chemotherapy to these patients, who require attenuated doses of ara-C (1 g/m^2 vs. 3 g/m^2) and MTX (dose adjusted for creatinine clearance) to avoid excessive toxicity. Thus, strategies to improve outcome, particularly in the elderly, require use of modalities that do not impart additional toxicity.

The B-cell lineage restricted marker CD20 is highly expressed in BL and B-ALL. Impressive responses to single-agent rituximab have been observed in children with relapsed or refractory BL or B-ALL,[34] and its activity has been well established in several other lymphoproliferative disorders.[25–27] In vitro, rituximab sensitized NHL B-cell lines to chemotherapeutic drugs via selective down-regulation of antiapoptotic proteins Bcl-2 and Bcl-x_L.[35] Bcl-x_L protects cells from drug cytotoxicity, conferring a multidrug-resistant phenotype.[36] Down-regulation of Bcl-x_L by rituximab could modulate this effect and confer synergy. Thus, we hypothesized that a chemoimmunotherapy regimen using rituximab concurrently with hyper-CVAD could further improve the prognosis without additional toxicity.

In this study, the CR rate with hyper-CVAD plus rituximab was 86%, similar to the experience with hyper-CVAD alone.[17] The estimated 3-year survival, EFS, and DFS rates with hyper-CVAD plus rituximab were 89%, 80%, and 88%, respectively, improved overall when compared with hyper-CVAD (3-year survival 53%, $P < .01$; EFS 52%, $P = .02$; and DFS 60%, $P = .03$). The results were encouraging in the unfavorable elderly subgroup, as all survived the induction period with use of the protective environment (Table 4, Figs. 2, 3). In these 9 patients, the CR rate was 100%, and estimated 3-year survival and DFS rates were 89% and 88%, respectively. These results compared favorably with a DFS rate of 30% observed with hyper-CVAD ($P = .03$), without an apparent increase in toxicity.

The DFS rates reported in other adult B-ALL series with intensive chemotherapy regimens in younger patients (median ages, 30-36 yrs) ranged from 50% to 71% (Table 1).[10,16,18,21] Only 4% to 12% were aged ≥60 yrs, versus 29% of our patients. Although decrease in induction mortality influenced OS, a reduction in relapse rate was also observed in the elderly group compared with hyper-CVAD (0% vs. 50%, $P = .02$). A trend toward reduction in disease recurrence was also noted for those younger than 60 years (11% vs. 29%, $P = .11$). The incidence of CNS disease at presentation was similar to other reports (12-43%) and was not prognostic[13-19]; no isolated CNS relapses were observed. MVA of the entire study and historical group identified younger age and treatment with rituximab as factors associated with longer DFS, suggesting that addition of rituximab may be beneficial independent of supportive care (Fig. 1B).

Hoelzer et al.[37] reported preliminary results of a chemoimmunotherapy regimen for BL or B-ALL in the elderly. Twenty-six patients aged ≥ 55 years received chemotherapy plus rituximab (375 mg/m^2 i.v. Day 1 of Cycles 1-6, then 2 single doses) by Protocol B-NHL2002. Outcome was compared with an histori-

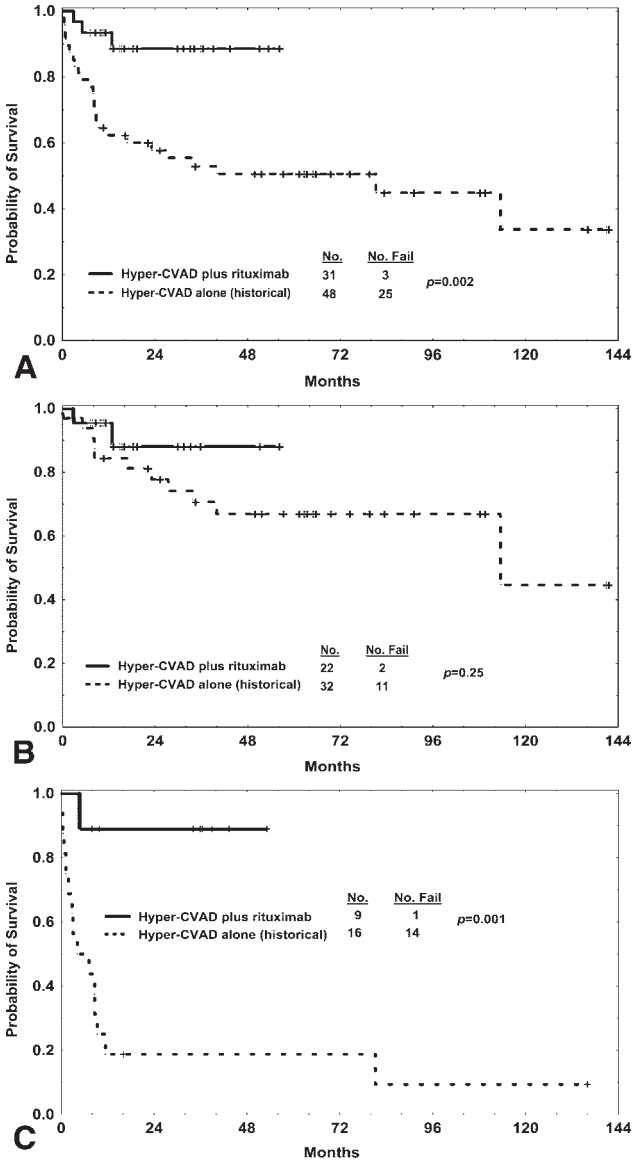

FIGURE 2. Survival with hyper-CVAD plus rituximab compared with hyper-CVAD, (A) overall, (B) age $<$ 60 years, (C) age $\geq$ 60 years.

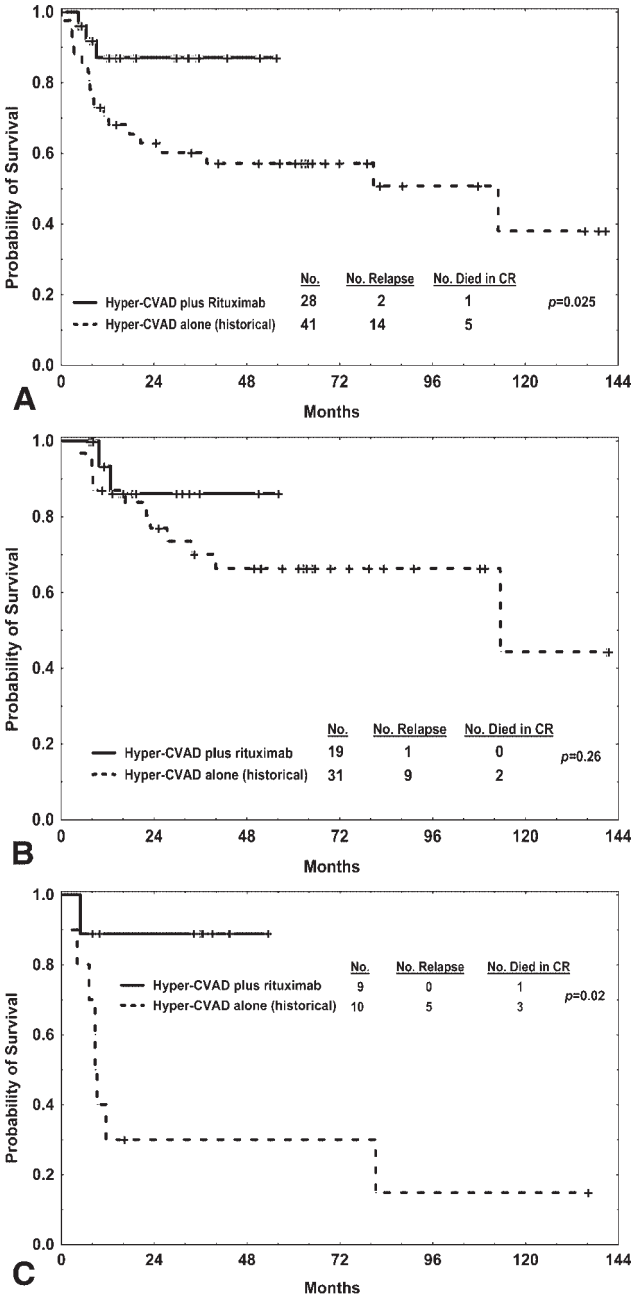

FIGURE 3. Disease-free survival (DFS) with hyper-CVAD plus rituximab compared with hyper-CVAD, (A) overall, (B) age $<$ 60 years, (C) age $\geq$ 60 years.

cal cohort of 45 patients treated with similar chemotherapy without rituximab (Protocol B-NHL90). The CR rate improved from 71% to 81%; survival rates were better with rituximab although follow-up was short (estimated 18-mo survival rate 84% vs. 6-yr survival rate 39%; $P = .03$).

The role of consolidative autologous or allogeneic SCT in BL or B-ALL is questionable because most may be cured with dose-intensive chemotherapy alone.[38,39] With our prior hyper-CVAD experience, relapses occurred quickly, with patients dying of disease before SCT strategies could be applied.[17] None of the patients in this report had SCT as consolidation after achieving CR. However, a few patients with progression after hyper-CVAD plus rituximab were able to receive salvage chemotherapy and subsequently undergo allogeneic SCT, suggesting that upfront addition of rituximab to intensive chemotherapy may alter the natural course of resistant or recurrent disease.

In summary, the hyper-CVAD plus rituximab chemoimmunotherapy regimen appeared promising for

TABLE 5
Remission Duration and DFS in BL or B-ALL in CR with hyper-CVAD with or without Rituximab

Characteristics	No. Pts (%)	% 3-year CRD	% 3-year DFS	Univariate *P* (log-rank)	Multivariate *P*†
Total group*	69	—	—	—	
Age, y				.03	.0004
< 60	50 (72)	77	75	—	
≥ 60	19 (28)	71	57	—	
Zubrod performance status				NS	
0-1	46 (67)	77	70	—	
2-3	23 (33)	70	70	—	
WBC, $\times 10^9$/L				.01	
< 25	60 (87)	79	76	—	
≥ 25	9 (13)	35	26	—	
Hemoglobin, g/dL				NS	
< 10	33 (48)	73	69	—	
≥ 10	36 (52)	77	73	—	
PLT, $\times 10^9$/L				.001	
< 150	38 (55)	59	53	—	
≥ 150	31 (45)	96	93	—	
% Peripheral blasts				.01	
0	38 (55)	88	85	—	
≥ 1	31 (45)	60	53	—	
% Bone marrow blasts				.02	
< 50	28 (43)	81	81	—	
≥ 50	37 (57)	67	58	—	
Lactate dehydrogenase, U/L				.001	
< 5000	46 (68)	84	80	—	
≥ 5000	22 (32)	56	49	—	
Disease state				.001	
BL	22 (32)	95	95	—	
B-ALL	47 (68)	67	60	—	
Morphology				NS	
Burkitt	51 (74)	72	65	—	
Burkitt-like	18 (26)	87	87	—	
Karyotype				.01	
t(8;14), t(2;8) or t(8;22)	24 (44)	81	70	—	
t(14;18) or 14q32 only	5 (9)	60	40	—	
Hyperdiploid or diploid	22 (41)	82	82	—	
Pseudodiploid or other	3 (6)	33	33	—	
B_2 microglobulin, mg/dL				.01	
< 3	26 (45)	86	86	—	
≥ 3	32 (55)	62	53	—	
CNS leukemia				NS	
Yes	59 (86)	78	72	—	
No	10 (14)	60	60	—	
Extramedullary disease other than CNS				.01	
Yes	44 (64)	67	61	—	
No	25 (36)	91	91	—	
Gastrointestinal disease				.03	
Yes	52 (75)	70	64	—	
No	17 (25)	94	94	—	
Protective environment				NS	
Yes	7 (10)	100	86	—	
No	62 (90)	73	69	—	
Hyper-CVAD				.02	.003
With rituximab	28 (41)	91	88	—	
Without rituximab	41 (59)	66	60	—	

CRD: complete response duration; DFS: disease-free survival; NS: not significant; CNS: central nervous system; MVA: multivariate analysis; —: not included in MVA.

* Three patients had resected disease.

† MVA shown for DFS.

BL and B-ALL, particularly in the elderly, similar to improved outcomes observed with other frontline chemoimmunotherapy regimens (e.g., CHOP plus rituximab for non-Burkitt NHL[28,40] and fludarabine, cyclophosphamide plus rituximab for CLL[41]). These preliminary results suggest that additional studies are warranted. Other single-arm Phase II clinical trials of rituximab given concurrently with intensive chemotherapy for BL and B-ALL are underway (e.g., B-NHL2002[37] and Cancer and Leukemia Group B [CALGB] study[1]). Results of these and other studies (perhaps a randomized trial) are needed to define the role and optimal use of rituximab for BL and B-ALL.

REFERENCES

1. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. *Blood*. 2004;104:3009-3020.
2. Thomas DA, Cortes J, Bueso-Ramos C, Kantarjian HM, Hagemeister FB. High grade non-Hodgkin's lymphomas. In: Grossbard ML, editor. *Malignant Lymphomas*. New York: BC Decker Inc, 2002:152-197.
3. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976;33: 451-458.
4. Faderl S, Kantarjian HM, Talpaz M, Estrov Z. Clinical significance of cytogenetic abnormalities in adult acute lymphoblastic leukemia. *Blood*. 1998;91:3995-4019.
5. Gladstone B, Kadam PR, Balsara BR, et al. Cytogenetic studies on patients of acute lymphoblastic leukemia Burkitt's type with (8;14) & (14;18) translocations. *Indian J Med Res*. 1994;99:264-266.
6. Stamatoullas A, Buchonnet G, Lepretre S, et al. De novo acute B cell leukemia/lymphoma with t(14;18). *Leukemia*. 2000;14:1960-1966.
7. Bernasconi C, Brusamolino E, Pagnucco G, Bernasconi P, Orlandi E, Lazzarino M. Burkitt's lymphoma/leukemia: a clinicopathologic study on 24 adult patients. *Leukemia*. 1991;5(suppl 1):90-94.
8. Ostronoff M, Soussain C, Zambon E, et al. Burkitt's lymphoma in adults: a retrospective study of 46 cases. *Nouv Rev Fr Hematol*. 1992;34:389-397.
9. Kantarjian HM, Walters RS, Keating MJ, et al. Results of the vincristine, doxorubicin, and dexamethasone regimen in adults with standard- and high-risk acute lymphocytic leukemia. *J Clin Oncol*. 1990;8:994-1004.
10. Magrath IT, Janus C, Edwards BK, et al. An effective therapy for both undifferentiated (including Burkitt's) lymphomas and lymphoblastic lymphomas in children and young adults. *Blood*. 1984;63:1102-1111.
11. Murphy SB, Bowman WP, Abromowitch M, et al. Results of treatment of advanced-stage Burkitt's lymphoma and B cell (SIg+) acute lymphoblastic leukemia with high-dose fractionated cyclophosphamide and coordinated high-dose methotrexate and cytarabine. *J Clin Oncol*. 1986;4:1732-1739.
12. Bowman WP, Shuster JJ, Cook B, et al. Improved survival for children with B-cell acute lymphoblastic leukemia and stage IV small noncleaved-cell lymphoma: a pediatric oncology group study. *J Clin Oncol*. 1996;14:1252-1261.
13. Patte C, Philip T, Rodary C, et al. High survival rate in advanced-stage B-cell lymphomas and leukemias without CNS involvement with a short intensive polychemotherapy: results from the French Pediatric Oncology Society of a randomized trial of 216 children. *J Clin Oncol*. 1991;9:123-132.
14. Reiter A, Schrappe M, Parwaresch R, et al. Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage—a report of the Berlin-Frankfurt-Munster Group. *J Clin Oncol*. 1995;13: 359-372.
15. Reiter A, Schrappe M, Ludwig WD, et al. Favorable outcome of B-cell acute lymphoblastic leukemia in childhood: a report of three consecutive studies of the BFM group. *Blood*. 1992;80:2471-2478.
16. Hoelzer D, Ludwig WD, Thiel E, et al. Improved outcome in adult B-cell acute lymphoblastic leukemia. *Blood*. 1996;87: 495-508.
17. Thomas DA, Cortes J, O'Brien S et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. *J Clin Oncol*. 1999;17:2461-2470.
18. Soussain C, Patte C, Ostronoff M, et al. Small noncleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. *Blood*. 1995;85:664-674.
19. Todeschini G, Tecchio C, Degani D, et al. Eighty-one percent event-free survival in advanced Burkitt's lymphoma/leukemia: no differences in outcome between pediatric and adult patients treated with the same intensive pediatric protocol. *Ann Oncol*. 1997;8(suppl 1):77-81.
20. Rizzieri DA, Johnson JL, Niedzwiecki D, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: final results of Cancer and Leukemia Group B Study 9251. *Cancer*. 2004;100:1438-1448.
21. Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. *Ann Oncol*. 2002;13: 1264-1274.
22. Di Nicola M, Carlo-Stella C, Mariotti J, et al. High response rate and manageable toxicity with an intensive, short-term chemotherapy programme for Burkitt's lymphoma in adults. *Br J Haematol*. 2004;126:815-820.
23. Hoelzer D, Arnold R, Diedrich H, et al. Successful treatment of Burkitt's NHL and other high-grade NHL according to protocol for mature B-ALL [abstract]. *Blood*. 2002;100:159a. Abstract 595.
24. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;329:987-994.
25. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825-2833.
26. O'Brien SM, Kantarjian H, Thomas DA, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J Clin Oncol*. 2001;19:2165-2170.
27. Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *J Clin Oncol 15*. 2001;19:2153-2164.

28. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235-242.
29. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. *Cancer*. 2002;94:1492-1499.
30. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc*. 1965;53:457-481.
31. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *J R Stat Soc*. 1966;50:163-170.
32. Fleming TR, Harrington DP. *CountingProcesses and Survival Analysis*. New York: Wiley, 1991.
33. Cox DR. Regression models and life tables. *J R Stat Soc*. 1972;34:187-220.
34. de Vries MJ, Veerman AJ, Zwaan CM. Rituximab in three children with relapsed/refractory B-cell acute lymphoblastic leukaemia/Burkitt non-Hodgkin's lymphoma. *Br J Haematol*. 2004;125:414-415.
35. Jazirehi AR, Gan XH, De Vos S, Emmanouilides C, Bonavida B. Rituximab (anti-CD20) selectively modifies Bcl-xL and apoptosis protease activating factor-1 (Apaf-1) expression and sensitizes human non-Hodgkin's lymphoma B cell lines to paclitaxel-induced apoptosis. *Mol Cancer Ther*. 2003;2:1183-1193.
36. Tudor G, Aguilera A, Halverson DO, Laing ND, Sausville EA. Susceptibility to drug-induced apoptosis correlates with differential modulation of Bad, Bcl-2 and Bcl-xL protein levels. *Cell Death Differ*. 2000;7:574-586.
37. Hoelzer D, Goekbuget N, Beck J, et al. Subtype adjusted therapy improves outcome of elderly patients with acute lymphoblastic leukemia (ALL) [abstract]. *Blood*. 2004;104:Abstract 2732.
38. Sweetenham JW, Pearce R, Taghipour G, Blaise D, Gisselbrecht C, Goldstone AH. Adult Burkitt's and Burkitt-like non-Hodgkin's lymphoma-outcome for patients treated with high-dose therapy and autologous stem-cell transplantation in first remission or at relapse: results from the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 1996;14:2465-2472.
39. Nademanee A, Molina A, O'Donnell MR et al. Results of high-dose therapy and autologous bone marrow/stem cell transplantation during remission in poor-risk intermediate- and high-grade lymphoma: international index high and high-intermediate risk group. *Blood*. 1997;90:3844-3852.
40. Vose JM, Link BK, Grossbard ML, et al. Phase II study of rituximab in combination with chop chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2001;19:389-397.
41. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23:4079-4088.