Hyper-CVAD Program in Burkitt's-Type Adult Acute Lymphoblastic Leukemia

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Purpose: **To evaluate response and outcome with a front-line intensive multiagent chemotherapy regimen in adults with Burkitt's-type acute lymphoblastic leukemia (B-ALL).**

Patients and Methods: **From September 1992 to June 1997, 26 consecutive adults with newly diagnosed untreated B-ALL received hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD). Their median age was 58 years (range, 17 to 79 years), and 46% were ≥ 60 years. Patients received Hyper-CVAD alternated with courses of high-dose methotrexate and cytarabine. Granulocyte colony-stimulating factor and prophylactic antibiotics were administered for all eight planned courses. CNS prophylaxis alternated intrathecal methotrexate and cytarabine on days 2 and 7 of each course.**

Results: **Complete remission (CR) was obtained in 21 patients (81%). There were five induction deaths (19%). The median time to CR was 22 days (range, 15 to 89 days); 70% achieved CR within 4 weeks. The 3-year survival rate was 49% (± 11%); the 3-year continuous CR rate was 61% (± 11%). Twelve CR patients (57%) were in continuous CR at a median follow-up of 3+ years (range, 13+ months to 6.5+ years). Characteristics predicting for worse survival were age ≥ 60 years, poor performance status, anemia, thrombocytopenia, peripheral blasts, and increased lactate dehydrogenase level. The 3-year survival rate was 77% for 14 patients younger than 60 years and 17% for 12 patients ≥ 60 years ($P < .01$). Regression analysis identified older age, anemia, and presence of peripheral blasts as independent factors associated with shorter survival. Patients could be stratified according to (1) no or one adverse feature, (2) two adverse features, and (3) all adverse features. The 3-year survival rates were 89%, 47%, and 0%, respectively ($P < .01$).**

Conclusion: **Hyper-CVAD is effective in adult B-ALL. Identification of patients with high risk for relapse and improved methods to detect residual disease may result in risk-oriented approaches.**

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BURKITT'S-TYPE ADULT acute lymphoblastic leukemia (B-ALL) is recognized as the L3 morphologic subtype of ALL as defined by the French-American-British (FAB) classification.[1] It accounts for 2% to 4% of adult ALL cases. B-ALL is a high-grade malignancy, has an aggressive clinical course, and is composed of small noncleaved mature B lymphoid cells with rapid proliferative rates. In addition to its characterization by blast morphology, it is recognized by the presence of monoclonal surface immunoglobulins (sIgs), mature B-cell immunophenotype, and the characteristic translocations that involve chromosome 8 [t(8;14)(q24;q32) or the variants t(2;8)(p12;q24) and t(8;22)(q24;q11)].[2] These chromosomal aberrations lead to rearrangements and inappropriate expression of the proto-oncogene c-*myc* located at band 8q24 [translocations of the Ig heavy chain (IgH) gene locus on chromosome 14q32 in t(8;14), of the Ig kappa (Igκ) gene on chromosome 2p12 in t(2;8), and of Ig lambda (Igλ) gene on chromosome 22q11 in t(8;22) distal to c-*myc*].[3] Some mature B-ALL cases are classified as L1 or L2 morphologically because they fail to meet L3 FAB criteria but exhibit sIg expression and the characteristic chromosomal abnormalities.[4,5] They may be treated as B-ALL with similar responses and prognosis. Karyotypes observed in some B-cell lymphomas such as t(14;18)(q32;q21) are also found in B-ALL.[6] These may occur in association with the characteristic Burkitt's karyotype and may confer a worse prognosis; some investigators have reported an increased frequency of t(14;18) in older patients with adult B-ALL.[7,8]

Conventional ALL therapies in childhood and adult B-ALL yielded poor results. Complete remission (CR) rates ranged from 0% to 67%, and disease-free survival rates were 0% to 33%.[9-16] In the early 1980s, investigators used short-term dose-intensive chemotherapy programs that incorporated variations of high doses of cyclophosphamide, cytarabine (ara-C), and methotrexate (MTX).[17-23] Unprecedented CR rates of 89% to 92% were achieved in children, with disease-free survival rates of 50% to 87%. Reduction in the incidence of CNS relapses was also noted with increasing doses of MTX and ara-C and with intensive prophylactic intrathecal therapy with or without cranial irradiation.

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Prophylactic cranial irradiation was initially used but was later discontinued because of concerns of delayed neurologic sequelae.

Application of similar programs in adult B-ALL resulted in improved CR rates of 63% to 79%, disease-free survival rates of 50% to 65%, and survival rates of 49% to 54%.[16,24,25] Recently, outcome with adult B-ALL in our institution has been improved by modifying a program designed by Murphy et al[22] for childhood B-ALL. This report summarizes the results with this modified regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) as front-line therapy for adult B-ALL.

PATIENTS AND METHODS

Study Group

Twenty-six consecutive adults with newly diagnosed, untreated B-ALL referred to M.D. Anderson Cancer Center (Houston, TX) received Hyper-CVAD between September 1992 and June 1997. Informed consent was obtained according to institutional guidelines. Eligibility criteria were age $\geq$ 15 years and confirmed diagnosis of B-ALL. There were no restrictions by performance status, older age, or organ dysfunction. Six cases of human immunodeficiency virus–positive B-ALL treated with Hyper-CVAD are reported separately.[26] All patients were required to have a documented morphologic diagnosis of ALL (with $\geq$ 25% blasts in the bone marrow or $\geq 10 \times 10^9$ peripheral blasts/L) confirmed by enzymatic stain analysis (negative myeloid and monocytic stains). Burkitt's subtype was identified by: (1) L3 morphology (FAB classification); or (2) presence of the characteristic cytogenetic translocations [t(8;14)(q24;q32) or variants t(2;8)(p12;q24) and t(8;22)(q24;q11)] or c-*myc* rearrangement at the molecular level in cases lacking cytogenetic data; and (3) mature B-cell immunophenotype (sIg positivity $>$ 20% or κ/λ light-chain clonality with B-lineage–associated antigens CD19 or CD20).

Work-up at diagnosis included a history with physical examination and documentation of disease in extramedullary sites (confirmed by imaging and appropriate cytologic or histologic evaluations): lumbar punctures for CSF cytologic analysis were performed at diagnosis concomitant with prophylactic intrathecal chemotherapy administration to evaluate asymptomatic disease. Baseline chest radiographs were performed in all patients; those with abnormalities underwent further imaging with computed tomography. Magnetic resonance imaging and/or computed tomography of the brain was performed in all patients with cranial nerve abnormalities or positive CNS cytology. Computed tomography of the abdomen/pelvis was performed in all but one patient (ultrasound was performed secondary to increased creatinine level) to evaluate hepatosplenic abnormalities and extramedullary disease. Laboratory evaluation included complete blood counts, differential and platelet counts, sequential multiple analysis (SMA 12) with liver and renal function studies, and coagulation profiles. Bone marrow aspirate and biopsy specimens were analyzed with (1) modified Wright's stain for morphology; (2) cytochemical stains for myeloperoxidase, chloroacetate, nonspecific esterase, periodic-acid Schiff, and terminal deoxynucleotidyl transferase (Tdt); (3) immunophenotyping for B-cell lineage antigens and sIg; and (4) karyotyping. Marrow aspiration was performed at diagnosis, on days 14 and 21 of the induction phase (course 1), and at CR. Subsequent aspirations were repeated every two to three courses thereafter until therapy was completed, followed by surveillance marrows every 3 months in the first year and every 6 months thereafter.

Therapy

Therapy consisted of eight courses of alternating intensive chemotherapy. Odd courses (1, 3, 5, and 7) consisted of Hyper-CVAD: (1) hyperfractionated cyclophosphamide 300 mg/m^2 intravenously (IV) over 2 hours every 12 hours for six doses on days 1 to 3, with mesna 600 mg/m^2/d IV via continuous infusion on days 1 to 3 beginning 1 hour before cyclophosphamide and completed by 12 hours after the last dose of cyclophosphamide; (2) vincristine 2 mg IV on days 4 and 11; (3) doxorubicin 50 mg/m^2 IV over 2 hours via central venous catheter on day 4; and (4) dexamethasone 40 mg daily either orally or IV on days 1 to 4 and days 11 to 14. The first course was accompanied by appropriate IV hydration and alkalinization (eg, dextrose in one-half normal saline plus sodium bicarbonate 100 mEq/L, to run at 100 to 150 mL/h, ie, 2.5 to 3 L/d; furosemide 20 to 40 mg was administered every 12 to 24 hours to keep adequate intake–output) and allopurinol to reduce the incidence of tumor lysis syndrome. Even courses (2, 4, 6, and 8) consisted of MTX and ara-C: MTX 1 g/m^2 IV over 24 hours on day 1, and ara-C 3 g/m^2 over 2 hours every 12 hours for four doses on days 2 and 3. Intravenous alkalinization was used to promote excretion of MTX in all courses. Calcium leucovorin was administered at a dose of 50 mg IV starting 12 hours after the completion of MTX and continued at a dose of 15 mg IV every 6 hours for eight doses until MTX blood levels were less than 0.1μmol/L. An algorithm of additional leucovorin rescue (50 mg IV every 6 hours) was followed if MTX blood levels were elevated (monitored at end of infusion [0 hour] $>$ 20μmol/L, 24 hours $>$ 1μmol/L, 48 hours $>$ 0.1μmol/L). The IV formulation was supplemented with oral sodium bicarbonate on days 1 to 3. Oral acetazolamide was used to promote excretion if the urine pH was less than 7.0.

Standard dose reductions were as follows: (1) ara-C to 1 g/m^2 for age $\geq$ 60 years, creatinine level greater than 2 g/dL, or MTX level at 0 hour more than 20μmol/L; (2) vincristine to 1 mg for total bilirubin level greater than 2 g/dL; (3) doxorubicin by 25% for bilirubin level 2 to 3 g/dL, by 50% for bilirubin level 3 to 4 g/dL, and by 75% for bilirubin level greater than 4 g/dL; (4) MTX by 50% for creatinine level greater than 2 g/dL, by 75% for creatinine level greater than 3 g/dL, or by 50% to 75% for delayed excretion and/or nephrotoxicity with a previous course (the degree of reduction dependent on the severity); and (5) elimination of doxorubicin in the first course in patients with small bowel or gastric involvement to reduce the length of myelosuppression and risk of perforation (n = 3).

Granulocyte colony-stimulating factor was initiated at least 24 hours after chemotherapy was completed at a dose of 10μg/kg subcutaneously daily and continued until the total WBC count was $\geq 3 \times 10^9$/L. Dose-intensity was maintained with subsequent courses initiated when the total WBC count was $\geq 3 \times 10^9$/L and the platelet count was $\geq 60 \times 10^9$/L after a waiting period of 24 hours after discontinuation of granulocyte colony-stimulating factor. If the WBC count was $\geq 3 \times 10^9$/L but the platelet count was less than 60×10^9/L on day 21, granulocyte colony-stimulating factor administration was held if the WBC count reached 30×10^9/L and hematologic profiles were obtained every 3 days until platelet recovery. Completion of eight courses on a schedule of every 21 days or earlier if count recovery occurred (but at least 14 days from the last course) would be expected to take 5 to 6 months. No maintenance therapy was administered.

CNS prophylaxis included alternating intrathecal administrations of MTX 12 mg (6 mg only via Ommaya) on day 2 and ara-C 100 mg on day 7 of each course for all eight courses (16 intrathecal injections).[27]

Therapy for CNS leukemia resulted in augmentation of intrathecal therapy during the induction course to twice weekly until the CSF cell count was normalized and the cytologic examination was negative for evidence of malignant cells; the program was then resumed as for prophylactic therapy. No prophylactic cranial irradiation (XRT) was administered, although therapeutic XRT could be administered if indicated. Four patients received therapeutic XRT to the base of the skull with 30 Gy administered over 2 weeks in addition to intrathecal therapy for documented CNS involvement and cranial nerve palsy. Other extramedullary sites of disease were treated as appropriate; one patient received consolidation XRT to a lytic lesion of the femur.

Supportive Care

Patients received oral prophylactic antibiotic therapy with either a quinolone (ciprofloxacin 500 mg twice daily or levofloxacin 500 mg daily) or trimethoprim-sulfamethoxazole double strength one tablet twice daily for antibacterial coverage, fluconazole 200 mg daily for antifungal coverage, and acyclovir 200 mg twice daily (or valacyclovir 500 mg daily) for mucositis prophylaxis with antiviral coverage. Hematologic profiles were obtained at least biweekly; appropriate transfusion support was provided with packed RBCs given for symptomatic and/or severe anemia, and platelet transfusions were given prophylactically for a platelet count $\leq 15 \times 10^9$/L or $\leq 50 \times 10^9$/L with evidence of hemorrhage. All blood products were irradiated. Neutropenic episodes generally resulted in hospitalization and initiation of broad-spectrum parenteral antibiotics followed by amphotericin B if clinically applicable. Granulocyte transfusions were initiated in patients with prolonged neutropenia and documented evidence of progressive life-threatening infection despite appropriate antibiotic and antifungal therapy.

Response Criteria

CR was defined as $\leq$ 5% blasts in a normocellular or hypercellular marrow with a granulocyte count greater than 1.5×10^9/L and a platelet count greater than 100×10^9/L for at least 4 weeks. Complete resolution of extramedullary disease was required for a CR. Other response outcomes were defined as induction death if death occurred after start of therapy without meeting the definition of CR or resistant disease, and as resistant disease if the patient survived the treatment period but the leukemia persisted or regrew. Relapse was defined as disease recurrence at any site after achievement of CR; assessments were performed periodically with physical examinations, laboratory evaluations (including bone marrow aspirations), and radiography every 2 to 3 months for the first year after completion of therapy, every 4 to 6 months for the second year, every 6 months for the third year, and annually thereafter. Toxicity was evaluated according to National Cancer Institute criteria.

Statistical Methods

Differences in response rates by pretreatment characteristics among subgroups were analyzed by χ^2 or Fisher's exact tests. Survival was measured from the date of initiation of therapy until death from any cause. CR duration was measured from the date of CR until documented relapse. Toxic deaths in CR were considered as failures at the time of death on the remission duration curves; thus, CR duration and disease-free survival for patients who achieved CR were interchangeable in this analysis. A cutoff date of June 30, 1998, was established for analyzing the data for this report. Survival and remission duration curves were plotted according to the methods of Kaplan and Meier, with differences among them analyzed by the log-rank test.[28] Factors significant for response and survival outcomes by univariate analysis were analyzed further by stepwise regression using the assumption of proportional hazards as suggested by Cox.[29]

RESULTS

Study Group

Patient characteristics are listed in Table 1. The median age was 58 years (range, 17 to 79 years; median age for patients $<$ 60 years, 38 years), 46% of the patients were $\geq$ 60 years, and 81% were male. The median hematologic parameters were as follows: WBC count 7.2×10^9/L (range, 1.8 to 67.4×10^9/L), hemoglobin level 9.2 g/dL (range, 5.4 to 15 g/dL), platelet count 47×10^9/L (range, 13 to 396×10^9/L), absolute peripheral blasts 7×10^9/L (range, 0 to 80×10^9/L), and bone marrow blasts 75% (range, 16% to 98%; one patient had $<$ 25% blasts but $> 10 \times 10^9$/L circulating blasts). Median lactate dehydrogenase (LDH) level was 5,635 U/L (range, 649 to 42,001 U/L), median albumin level was 3.1 g/dL (range, 2.2 to 4.2 g/dL), and median total bilirubin level was 0.7 g/dL (range, 0.2 to 1.3 g/dL).

B-ALL features are listed in Table 2. Morphologic characteristics included the L3 FAB classification in all but three patients (all three were $>$ 90% sIg-positive, yet were

Table 1. Pretreatment Characteristics

Characteristic	Total		Age ≥ 60 Years	
	No.	%	No.	%
Total	26		12	
Female sex	5	19	4	33
Zubrod 3-4 performance status	6	23	4	33
Karyotype				
t(8;14), t(2;8), or t(8;22)*	10	38	3	25
t(14;18) or 14q32 only	4	15	3	25
Hyperdiploid/diploid	4	15	1	8
Insufficient metaphases	6	23	4	33
Not available	2	8	1	8
Age ≥ 60 years	12	46	—	
WBC count ≥ 10×10^9/L	7	27	3	25
Hemoglobin < 10 g/dL	17	65	9	75
Platelet count < 100×10^9/L	20	77	11	92
Peripheral blasts present	17	65	9	75
Marrow blasts ≥ 75%	11	42	6	50
LDH, U/L				
620-4,999	11	42	4	33
5,000-10,000	7	27	2	17
> 10,000	8	31	6	50
Albumin < 3 g/dL	9	37	7	58
Bilirubin ≥ 1.3 g/dL	3	12	2	17
Hepatomegaly	8	31	4	33
Splenomegaly	6	23	2	17
Peripheral adenopathy	5	19	2	17
CNS leukemia	11	42	6	50
Extramedullary disease (other than CNS)	14	54	6	50
Gastrointestinal disease	8	31	4	33

*Two patients with t(14;18) or 14q32 and B-ALL karyotype in same clone.

Table 2. Outcome by B-ALL Features: FAB, Immunophenotype, and Karyotype

Features	Outcome							
			% Age > 60	CR		Relapse		% 3-Year
	No.	%	Years	No.	%	No.	%	Survival
Total	26		46	21	81	9	43	49
L3, t(8;14), t(2;8), or t(8;22)	7	31	14	7	100	1	14	86
L3, CALLA, t(8;14), t(2;8), or t(8;22)	2	8	50	1	50	None		50
L3, other, slg+*	11	38	64	8	73	4	50	36
L3, CALLA, other, slg+†	3	12	33	3	100	2	67	33
L2, t(8;14), slg+ > 90%	1	4	All	1	100	All		None
L1/L2, other, slg+ > 90†	2	8	50	1	50	All		None

Abbreviation: CALLA, common ALL antigen.

*c-*myc* rearranged in 1 of 1 patient tested.

†c-*myc* rearranged in 2 of 2 patients tested.

classified as L1 or L2 with Burkitt's-like morphology). Histochemical stains were positive for periodic-acid Schiff in 29% and for Tdt in seven patients (27%; six Tdt-positive patients were FAB L3; one patient was FAB L2 with B-cell immunophenotype and c-*myc* rearrangement). Tdt positivity in B-ALL has been reported in other series.[16] Five patients had common ALL antigen–positive immunophenotype. The median CD20 expression was 61% (range, 3% to 95%). Cytogenetic analysis (n = 24) showed the characteristic translocations of B-ALL or add(8)(q24) in 10 (38%) of the patients; in six patients (26%), t(14;18)(q32;q31) or add(14)(q32) was detected (two in association with the B-ALL karyotype). Hyperdiploidy was usually present with the aforementioned abnormalities (n = 7) in addition to deletions and additions of multiple other various chromosomes (including 1q11 [n = 4] as reported in other series[3,30]) with the malignant clones. The chromosome 1 abnormalities were observed in patients younger than 50 years, whereas t(14;18)(q32;q31) or add(14)(q32) were observed in patients older than 50 years. Five of six patients tested had evidence of c-*myc* rearrangement; others (n = 4) had evidence of *JH* rearrangement. The patient with germline c-*myc* had L3 morphology and B-cell immunophenotype with hyperdiploid cytogenetics. Such heterogeneity has been observed by other investigators.[31-33]

Eighteen patients (69%) had extramedullary disease documented at presentation: (1) four with CNS (n = 3) or leptomeningeal disease (n = 1); (2) seven with CNS leukemia concurrently with other sites such as ascitic fluid (n = 1), lymph nodes (n = 3), stomach (n = 2), or paraspinal mass (n = 1); and (3) seven without CNS involvement but disease in the small bowel (n = 1), lymph nodes (n = 2), liver (biopsy-proven; n = 1), focal splenic lesions (n = 1), or bone (n = 2). Of the 11 patients (42%) with CNS disease, six (55%) had cranial nerve palsy or other neurologic findings (one with negative cytology), whereas five (45%) were asymptomatic with positive cytopathologic examination of the CSF.

Response

Twenty-one of 26 patients (81%) treated with Hyper-CVAD achieved CR; five (19%) died during induction, and none had refractory disease. The median time to CR from initiation of therapy was 22 days (range, 15 to 89 days); 70% achieved CR within 4 weeks. Five (24%) of the 21 patients required ≥ two courses to achieve CR, three of whom (60%) remained in continuous CR. All patients who achieved CR reverted to diploid karyotype by marrow cytogenetics. Unfavorable characteristics for achieving CR included female sex (induction deaths occurred in three of the five women), poor performance status, albumin level less than 3.0 g/dL, and presence of hepatomegaly or splenomegaly on physical examination ($P \leq .05$; for hepatomegaly, $P < .01$). Other characteristics, including age, WBC count, platelet count, percent marrow blasts, LDH level, immunophenotype, karyotype, and extramedullary (including CNS) disease were not associated with differences in CR rates.

The median time to induction death in five patients (19%) was 25 days (range, 19 to 60 days). Induction death occurred in one of 14 patients younger than 60 years versus four of 12 older patients (7% *v* 33%; $P = .23$). Thus, four (80%) of the five induction deaths were among patients ≥ 60 years of age; all five had a performance status of ≥ 2, albumin levels less than 3.0 g/dL, platelet counts ≤ 60×10^9/L, and hepatomegaly on physical examination. Multiorgan failure with sepsis syndrome secondary to documented fungal infection occurred in four of these patients despite appropriate antifungal prophylaxis and therapy; three had *Aspergillus* pneumonia, one had *Candida* bacteremia, and one had respiratory syncytial virus (RSV) identified by bronchoscopy as the etiology for progressive pneumonia. None of the five patients had developed tumor lysis syndrome. Only one patient had evidence of extramedullary involvement with extensive leptomeningeal disease that resulted in spinal cord necrosis and progressive paraplegia; subarachnoid hemorrhage, extensive bone marrow necrosis, and *Aspergillus* pneumonia contributed to his death. One patient seemed to be achieving a CR after two courses of hyper-CVAD with absence of marrow blasts and normalization of counts but died 2 days later secondary to overwhelming infections (from prolonged neutropenia), pancreatitis with hepatic failure (serum hepatitis B surface antigen was detected), and the ensuing multisystem organ failure.

Survival

The estimated median survival duration was 16 months (range, 1 month to 6.5+ years). There were five induction deaths (19%), and nine patients died (43%) after relapse secondary to refractory disease or infectious complications of salvage therapy. No patient died while in CR from treatment-related complications of consolidation therapy. The estimated 3-year survival rate was 49% (± 11%; Fig 1); patients younger than 60 years had an estimated 3-year survival rate of 77%. The 3-year continuous CR rate was 61% (± 11%; Fig 1). Twelve (57%) of the 21 patients who achieved CR remained alive in continuous CR at a median follow-up duration of 3.5+ years (range, 9+ months to 6.5+ years).

Factors associated with worse survival were female sex, older age, poor performance status, hemoglobin level less than 10 g/dL, platelet count less than 100×10^9/L, circulating blasts, and LDH level ≥ 5,000 U/L at presentation (Table 3). Survival was significantly better in patients younger than 60 years (77% *v* 17%; $P < .01$; Fig 2). The presence of peripheral blasts at diagnosis (n = 17) seemed to be a significant adverse feature. All five patients with induction deaths had detectable peripheral blasts, and eight (67%) of the 12 remaining patients who achieved CR have relapsed, whereas seven of eight patients (87%) without circulating blasts remained in CR ($P = .02$). No differences in survival were observed by WBC count, percent marrow blasts, bilirubin level, immunophenotype, karyotype, and organomegaly or extramedullary (including CNS) disease (data not shown in Table 3).

By multivariate analysis, characteristics associated with worse survival were age 60 ≥ years, hemoglobin level less than 10 g/dL, and presence of peripheral blasts (Table 3). Patients could be stratified into three groups: group 1, no or one adverse feature; group 2, two adverse features; and group 3, all adverse features. The 3-year survival rates for these groups were 89%, 47%, and 0%, respectively ($P < .01$).

Table 2 also lists outcome with Hyper-CVAD by B-ALL features (FAB subtype, immunophenotype, and karyotype). The best outcome was observed among patients in the first category, which included mostly patients younger than 60 years with all three typical features. In comparison, the 3-year survival rate for the older third group (same features except for other karyotypes) seemed inferior ($P = .03$). Patient numbers were too small to allow for further comparisons.

Treatment Delivery and Toxicity

The median number of total courses completed was 7.5 (range, one to eight); 13 (62%) of 21 remitters completed all eight planned courses, and 17 (81%) of 21 completed at least six courses. The median time to complete the planned program was 5.3 months (range, 3.5 to 6.6 months). Reasons for failure to complete the program were induction deaths (n = 5), relapse while on active therapy (n = 4), grade 3 cerebellar neurotoxicity (n = 1), psychiatric changes (severe

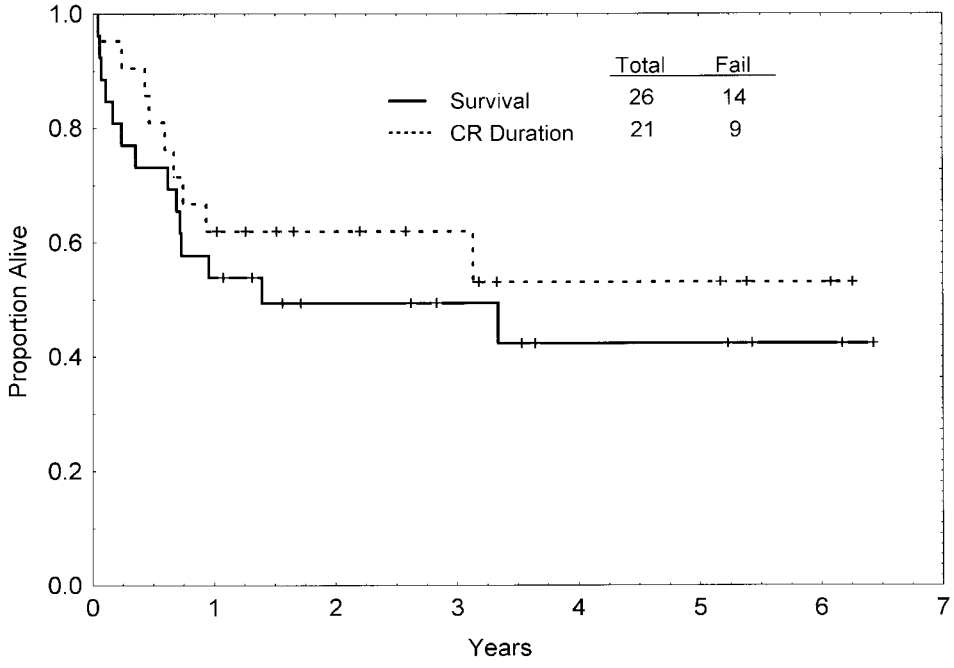

Fig 1. Survival and CR duration. Note all relapses but one occurred less than 1 year from CR.

Table 3. Survival by Pretreatment Characteristics and Number of Adverse Features

Characteristic	No. of Patients	% 3-Year Survival	*P* (log-rank)
Overall	26	49	—
Sex			
Male	21	55	< .05
Female	5	0	
Age, years			
< 60	14	77	< .01
≥ 60	12	17	
Zubrod Performance status			
1-2	20	60	< .01
3-4	6	0	
Hemoglobin, g/dL			
< 10	17	35	< .05
≥ 10	9	77	
Platelet count, × 10^9/L			
< 100	20	32	< .01
≥ 100	6	100	
Peripheral blasts			
Absent	9	88	< .05
Present	17	28	
LDH, U/L			
620-4,999	11	72	< .05
5,000-10,000	7	54	
> 10,000	8	0	
No. of adverse features*			
0 or 1	10	89	< .01
2	8	47	
3	8	0	

*Age ≥ 60 years, hemoglobin level < 10 g/dL, and circulating blasts.

depression with suicidal ideation) and diabetes insipidus (n = 1), thrombocytopenia without evidence of disease (n = 1), and noncompliance that resulted in delays in therapy and subsequent relapse (n = 1).

Dose reductions of MTX and/or ara-C occurred in 16 (76%) of 21 patients who received ≥ two courses. Patients older than 60 years (n = 12) underwent ara-C dose reduction from 3 g/m^2 to 1 g/m^2 by design to minimize the incidence of neurotoxicity; the development of subsequent grade 2 (n = 2) and grade 3 (n = 2) cerebellar neurotoxicity resulted either in further dose reductions or elimination of ara-C (with the substitution of the hyper-CVAD portion of the regimen). Dose reductions of MTX were required in four patients who developed tumor lysis syndrome during the induction phase and who required hemodialysis temporarily with eventual recovery of renal failure; in five patients with delayed MTX excretion and nephrotoxicity; and in four patients who developed grade 3 mucositis. The Hyper-CVAD courses (1, 3, 5, and 7) were generally given at 100% of the dose schedule, except for discontinuation of vincristine in five patients who developed peripheral neuropathy, and discontinuation of dexamethasone in four patients because of proximal myopathy. Cardiac toxicity was minimal (two episodes of atrial arrhythmias in the setting of an acute illness; no cases of cardiac failure). There were no significant differences observed in treatment-related toxicities, requirement for additional dose reductions (although a higher proportion of patients aged ≥ 60 years required reductions), or treatment delivery by age (Table 4).

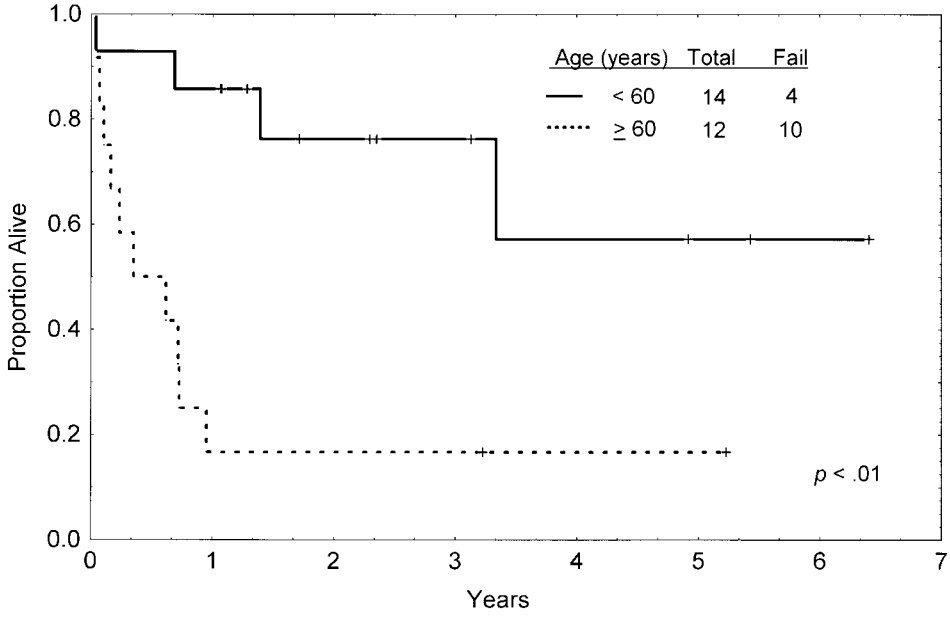

Fig 2. Survival by age.

Table 4. Toxicity and Treatment Delivery by Age in Patients Who Achieved CR

Parameter	Age < 60 Years (n = 13) No.	%	Age ≥ 60 Years (n = 8) No.	%	P (χ^2)
Completion ≥ 6 courses	11	85	6	75	NS
% Delay > 7 days of ≥ 2 courses	2	15	5	62	.08
Dose reduction					
Any	9	69	7	88	NS
Early (≤ course 4)	4	31	5	62	NS
Late (> course 4)	5	38	2	25	
MTX	2	15	3	38	NS
ara-C (additional)	7	54	4	50	
Vincristine	2	15	3	38	
Nephrotoxicity					
Increased creatinine > 2× with MTX	3	23	1	12	NS
Tumor lysis first course	1	8	2	25	NS
Neurotoxicity grade III-IV	2	15	2	29	NS
Infection with course 2	7	54	3	38	NS
Median number days to:					
CR	22		22		
Granulocytes > 0.5×10^9/L					
Course 2	14		15		
Course 3	15		16		
Platelets > 60×10^9/L					
Course 2	18		20		
Course 3	16		21		
Median no. of courses completed	8		7.5		
Median time to complete 8 courses, months	5		5.75		

Grade 3 to 4 hematopoietic toxicity was universal. Median time to recovery of the absolute neutrophil count to more than 0.5×10^9/L was 17 days (range, 12 to 28 days) and of the platelet count to more than 60×10^9/L was 20 days (no suppression beyond 35 days) for course 1 in all assessable patients (n = 21). Similar results were obtained with subsequent courses, although platelet recovery was slower with MTX/ara-C courses. Twelve episodes (8% incidence) of thrombocytopenia-related hemorrhage occurred in 152 assessable courses: retinal (n = 2), gastrointestinal (n = 2), CNS (n = 2, with one fatal subarachnoid hemorrhage), pulmonary (n = 1), severe epistaxis (n = 4), and antecubital hematoma (n = 1).

Myelosuppression-associated infectious complications were common despite the short duration of granulocyte counts less than 0.5×10^9/L (median of 6 days per course; range, 0 to 13 days). Incidence of neutropenic febrile episodes during the induction phase was 86% for 37 assessable courses: four episodes (11%) of sepsis; 12 episodes (32%) of pneumonia with three fungal, three bacterial, one RSV, and five with unknown pathogens; one episode of bacterial meningitis; 14 episodes (38%) of fever of unknown origin; and one episode of herpes simplex virus infection. Neutropenic febrile rates for subsequent courses were 30% to 39% with Hyper-CVAD and 47% to 55% with MTX/ara-C. Twelve episodes (8%) of herpes simplex virus infections were observed in 152 assessable courses despite the use of prophylactic acyclovir, including severe disseminated facial lesions (n = 1) and perirectal ulcerations (n = 2).

No long-term sequelae were identified, although six patients in CR still had mild vincristine-related peripheral neuropathy at the time of this writing. No cases of secondary malignancy were detected. One patient developed RSV pneumonia 16 months after completion of the program. He required mechanical ventilation but recovered and remained alive and in continuous CR at 3 years. One patient received interferon alfa-2a for chronic active hepatitis C and remained in remission at 5 years.

Salvage Therapy

Nine of 21 patients (43%) relapsed after they achieved remission with Hyper-CVAD. The median time to relapse was 7 months (range, 1 month to 3 years). All relapses but one occurred less than 12 months from diagnosis. Four patients relapsed while on therapy (at 1, 3, 5, and 6 months from CR), and five relapsed while off therapy (at 7, 8, 9, 11 months, and 3 years from CR). The only patient with late relapse at 3 years had features at diagnosis that included FAB L1 with Burkitt's-like morphology, B-cell immunophenotype (sIg > 90%), and t(14;18)(q32;q21), t(14;19)(q24;13.3), del(17)(q25) karyotype with c-*myc* rearrangement on molecular analysis. No isolated CNS relapses were observed.

Two patients died before they could receive salvage therapy. Primary salvage chemotherapy regimens were administered in seven patients: two received Hyper-CVAD salvage, and five received other salvage regimens; no patient underwent bone marrow transplantation. No CRs were observed. Thus, all nine of these patients died, with a median survival duration of 1 month after relapse (range, 3 days to 5 months).

Historical Comparison

The historical comparison consisted of 47 consecutive patients with B-ALL who were treated with VAD[11,12] (n = 41) or other conventional ALL combination chemotherapy regimens (n = 6) from 1980 to 1992. Compared with VAD, Hyper-CVAD included fractionated cyclophosphamide and high-dose MTX. It also delivered a higher number of high-dose ara-C courses (4 *v* 1 or 2), and treatment was more dose-intensive (eight courses given in 5 months *v* one course every 1 month). In B-ALL, Hyper-CVAD did not include maintenance therapy and did not offer autologous or allogeneic stem-cell transplantation (SCT) intensification, unlike VAD (2 to 2.5 years of maintenance). VAD-treated patients

tended to be younger (median age, 49 years; 25% were ≥ 60 years), to have fewer circulating blasts (17% *v* 65%), and to have fewer elevated LDH levels greater than 5,000 U/L (21% *v* 58%; $P = .004$).

Outcome with VAD seemed inferior despite a younger age cohort with better features at presentation. The CR rate was 68% compared with 81% with Hyper-CVAD, and 17% of the patients were refractory to induction therapy. Induction death rates were similar (15% for VAD). The estimated 3-year continuous CR rate was better with Hyper-CVAD overall (61% *v* 25%; $P = .04$) and in patients younger than 60 years of age (3-year CR rates 83% *v* 27%; $P < .01$) but not in patients ≥ 60 years (3-year CR rates 25% *v* 17%; *P* not significant). Similarly, a trend of better 3-year survival rate was observed with Hyper-CVAD (49% *v* 21%; $P = .07$), especially for patients younger than 60 years (77% *v* 26%; $P < .01$), but not for older patients (17% *v* 8%; *P* not significant).

DISCUSSION

The outcome of childhood B-ALL with conventional ALL therapy was historically poor.[9-15] The development of short-term, intensive, alternating multiagent chemotherapy regimens in childhood B-ALL/lymphoma by investigators such as the French Pediatric Oncology Society,[17,18] the German Study Group for childhood ALL (Berlin-Frankfurt-Munster),[19,20] the United Kingdom Children's Cancer Study Group,[21] and the Pediatric Oncology Group[22,23] yielded unprecedented survival rates of 60% to 80% at 2 years.[17-23] Murphy et al[22] designed a program applying the hypothesis of Goldie and Coldman[34] and expounded on a theoretical relationship between dose-intensity and efficacy. Maximizing exposure of rapidly proliferating B-ALL malignant cells to drug by hyperfractionation of the alkylating agent, and use of different non–cross-resistance agents in tandem, formed the basis for the Total Therapy B program for childhood B-ALL.[23]

Hyper-CVAD is a modified Murphy-like regimen applied to adult B-ALL at our institution. Our CR rate of 81% was comparable to that obtained by Hoelzer et al[16] (63% and 74%; 56% for patients aged > 50 years) and Soussain et al[24] (79%) with intensive programs in younger adults with B-ALL (Table 5). No patient was refractory to Hyper-CVAD administered as front-line therapy, and no deaths in remission were observed. The estimated 3-year survival rate was 49% (± 11%) and the 3-year continuous CR rate was 61% (± 11%); for patients younger than 60 years, these rates were 77% and 83%, respectively. The disease-free survival rates in other series ranged from 50% to 71%; however, most patients in such series were younger (median ages, 30 to 36 years). Only 4% to 12% were ≥ 60 years, versus 42% of our patients. We have also demonstrated for the first time a highly significant association between older age and worse prognosis in B-ALL.[35] The estimated 3-year survival rate was 77% for patients younger than 60 years and 17% for those ≥ 60 years (Fig 2; $P < .01$). The worse outcome of older patients may be a result of a biologically different disease with or without its association with t(14;18), or lower treatment intensity and worse tolerance of intensive chemotherapy. Such patients received by design lower ara-C doses (1 g/m^2 instead of 3 g/m^2) because of a high incidence of systemic toxicity and neurotoxicity with high-dose ara-C (as observed in acute myeloid leukemia studies). Whether a higher ara-C dose schedule might have improved the prognosis of the older patients needs to be investigated while cautiously balancing the risk:benefit ratios.

The induction death rate (19%) with Hyper-CVAD was comparable to the 8% to 40% incidence in other series and was caused by infectious complications of myelosuppression.[16,24,25] The induction death rate with Hyper-CVAD for non–B-ALL was 6%.[36] Four of the five induction deaths with Hyper-CVAD were in patients aged ≥ 60 years, and two thirds of relapses were also in this age group. Most relapses occurred within 1 year, and no isolated CNS relapses were observed. Relapse rates for the published adult B-ALL series were similar; more than 90% of reported relapses occurred within 12 months.

The incidence of CNS disease at presentation (42%) in our study was also similar to other reports (12% to 63%).[13,16,24,25] In the past, CNS disease constituted the most

Table 5. Outcome for B-ALL Treated With Intensive Front-Line Regimens From 1980 to 1997

Protocol (years of therapy)	No. of Patients	Age (years)			% CR	% Induction Deaths	CR		Survival	
		Median	% ≥ 60	% ≥ 50			%	Years	%	Years
Protocol 3[25] (1981-1988)	8	32	12	—	87	12	66	2	58	2
LMB84,86,89[24] (1984-1991)	24	30	4	—	79	8	57	3	58	3
B-NHL83[16] (1983-1989)	24	33	0	—	63	8	50	8	49	8
B-NHL86[16] (1989-1993)	35	36	NR	31	74	9	71	4	51	4
Present study (1992-1997)	26	58	46	58	81	19	61	3	49	3
Age < 60 years	14	38	—	—	93	7	83	3	77	3

NOTE. Only B-ALL patients included in this table (some results extrapolated from data).
Abbreviation: NR, not reported.

dreaded complication in B-ALL. It was also a major cause of treatment failure and patient death both at presentation and at relapse. Intensive chemotherapy regimens have nearly eliminated the impact of CNS disease on B-ALL prognosis; therefore, it is no longer a significant treatment challenge. In fact, routine XRT is not necessary, except perhaps in the presence of cranial nerve root palsies, because most patients can undergo effective prophylaxis or treatment for active disease with intrathecal chemotherapy, reducing the incidence of CNS failures to 3% to 5%.[17-23]

In our study, older patients had a higher incidence of 14q and complex cytogenetic abnormalities. This was observed previously by Velangi et al[8] in 26 patients (median age, 61 years); eight of 14 older patients had t(14;18) or complex abnormalities. Stamatoullas et al[7] reported on four patients with t(14;18) and acute B-ALL; their ages ranged from 27 to 50 years, and they had aggressive disease and extremely poor outcome (there was evidence of both c-*myc* and *bcl*-2 rearrangement in all four). Further investigations are required to determine the influence of these karyotypes on the disease biology and their association with age.

The role, if any, of autologous or allogeneic SCT in B-ALL is highly questionable[37,38] because (1) most patients are either cured with dose-intensive chemotherapy or relapse quickly and die rapidly before any SCT strategies could be applied (as in our study); and (2) the patients at high risk for relapse and in most need of SCT are paradoxically the older patients who are often not eligible for SCT programs. Sweetenham et al[38,39] reported encouraging results with autologous SCT in Burkitt's lymphoma in first remission. However, many patients who underwent SCT may have already been cured without SCT. Allogeneic SCT was performed in nine patients with CNS disease at diagnosis and in first remission from intensive therapy for B-ALL; 78% were alive in continuous CR ranging from 1.5 to 5 years.[40] However, as shown in our study, CNS involvement at presentation is no longer an adverse prognosis factor. In the series by Hoelzer et al[16] and Soussain et al,[24] some patients underwent SCT. In the first study, six patients (median age, 26 years) underwent SCT (five allogeneic with four in first CR; one autologous): three patients were disease-free survivors at 2.4, 6.9, and 7 years. In the second study, eight patients underwent SCT in first CR: the 3-year overall survival rate was 57% for both stage IV Burkitt's lymphoma and B-ALL. These results were inferior to the 3-year survival rate of 73% in patients who did not undergo SCT. The observations of early relapse and poor outcome with salvage chemotherapy (median survival, 1 month from relapse) highlight the selective nature of patients reported to have undergone SCT for relapse,[8,37] because most patients (as in our study) would have relapsed and died before institution of SCT, which suggests that time lag and natural patient selection may affect outcome. None of the patients in our study underwent SCT as consolidation or salvage therapy due to early relapse before preparation for SCT, older age, or poor performance status.

In summary, the results of Hyper-CVAD were favorable except in high-risk (mostly older) patients. In this subgroup, alternative investigational and supportive care strategies need to be explored.

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