Results of Treatment With Hyper-CVAD, a Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia

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Purpose: **To evaluate the efficacy and toxicity of Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), a dose-intensive regimen, in adult acute lymphocytic leukemia (ALL).**

Patients and Methods: **Adults with newly diagnosed ALL referred since 1992 were entered onto the study; treatment was initiated in 204 patients between 1992 and January 1998. No exclusions were made because of older age, poor performance status, organ dysfunction, or active infection. Median age was 39.5 years; 37% were at least 50 years old. Mature B-cell disease (Burkitt type) was present in 9%, T-cell disease in 17%. Leukocytosis of more than 30 × 10^9/L was found in 26%, Philadelphia chromosome–positive disease in 16% (20% of patients with assessable metaphases), CNS leukemia at the time of diagnosis in 7%, and a mediastinal mass in 7%. Treatment consisted of four cycles of Hyper-CVAD alternating with four cycles of high-dose methotrexate (MTX) and cytarabine therapy, together with intrathecal CNS prophylaxis and supportive care with antibiotic prophylaxis and granulocyte colony-stimulating factor therapy. Maintenance in patients with nonmature B-cell ALL included 2 years of treatment with mercaptopurine, MTX, vincristine, and prednisone (POMP).**

Results: **Overall, 185 patients (91%) achieved complete remission (CR) and 12 (6%) died during induction therapy. Estimated 5-year survival and 5-year CR rates were 39% and 38%, respectively. The incidence of CNS relapse was low (4%). Compared with 222 patients treated with vincristine, doxorubicin, and dexamethasone (VAD) regimens, our patients had a better CR rate (91% *v* 75%, *P* < .01) and CR rate after one course (74% *v* 55%, *P* < .01) and better survival (*P* < .01), and a smaller percentage had more than 5% day 14 blasts (34% *v* 48%, *P* = .01). Previous prognostic models remained predictive for outcome with Hyper-CVAD therapy.**

Conclusion: **Hyper-CVAD therapy is superior to our previous regimens and should be compared with established regimens in adult ALL.**

J Clin Oncol 18:547-561.

PROGNOSIS IN childhood acute lymphocytic leukemia (ALL) has improved significantly.[1,2] With modern regimens, complete remission (CR) rates exceed 90% and cure rates are approximately 70%.

Adult ALL therapy has followed the leads in childhood ALL, but the results have been more modest. With current regimens analogous to those in childhood ALL, CR rates are approximately 75% and long-term disease-free survival (DFS) rates range from 20% to 35%.[3-13] Prognosis is associated with host and disease characteristics including age, performance status, organ function, leukemic-cell phenotype and karyotype, and the rapidity of leukemic-cell clearance and achievement of CR. Patients are divided by these features into patients with standard- or good-risk ALL (25% of patients), with expected DFS rates of more than 50% to 60%; and patients with poor-risk ALL (75% of patients), with expected DFS rates of 20% or less.[3,6-9,12] Philadelphia chromosome (Ph)-positive ALL represents 15% to 20% of adult ALL (35% to 50% of pre–B-cell, common acute lymphoblastic leukemia antigen [CALLA]-positive ALL) and has the worst prognosis, with DFS rates of less than 10% with chemotherapy and 10% to 35% with allogeneic stem-cell transplantation (SCT).[14-17]

Murphy et al[18] developed a short-term, dose-intensive regimen with alternating hyperfractionated cyclophosphamide therapy and high doses of cytarabine (ara-C) and methotrexate (MTX) for the treatment of childhood Burkitt-type or mature B-cell ALL. Such regimens have increased CR rates and DFS rates in childhood[19,20] and adult[21-23] mature B-cell ALL but have induced significant myelosuppression-associated morbidity and mortality, as well as renal and neurotoxic complications. Increasing dose-intensity has improved prognosis in childhood[24-31] and adult[32-36] ALL. Growth-factor support allowed use of dose-intensive regimens with acceptable toxicity in solid and hematologic cancer, including ALL.[37-44] Granulocyte colony-stimulating factor (G-CSF) may have additional antitumor effects through suppression of abnormal messages or gene products

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Submitted February 24, 1999; accepted September 9, 1999.

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0732-183X/00/1803-547

(eg, BCL-2), which may be related to disease pathophysiology.[45-48]

We report the results of use of the Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen in adult ALL. This regimen is a modified dose-intensive regimen, adapted from the one designed by Murphy et al,[18] and involves G-CSF supportive care.

PATIENTS AND METHODS

Study Group

Adults with newly diagnosed ALL were entered onto the study beginning in February 1992. Data from all patients who were entered onto the study and began treatment between February 1992 and January 1998 were included in the analysis, to allow for data maturation. Informed consent was obtained according to institutional guidelines. Entry criteria were (1) age at least 15 years and (2) absence of other active malignancy and expected consequent death within 12 months, or human immunodeficiency virus-1–positive status. No exclusions were made because of performance status; cardiac, hepatic, or renal function; or concomitant active infection.

ALL was diagnosed based on lymphoid morphology of blasts and when there were less than 3% myeloperoxidase-positive blasts by light microscopy and strong positivity for terminal deoxynucleotidyl transferase or periodic acid-Schiff–block positivity.[49] Immunophenotypic and electron-microscopic analysis were used to confirm the diagnosis in difficult cases.[50-53]

Pretreatment work-up included history taking and physical examination; complete blood cell, differential, and platelet counts; serum chemistries (sequential multiple analysis [SMA] 12/60), including liver and renal function studies; bone marrow aspiration for morphologic analysis and staining; biopsy; cytogenetic analysis; immunophenotyping; and electron-microscopic studies as previously described.[3,51-53] Karyotypic categories were according to previously reported nonrandom chromosomal abnormalities of defined significance in ALL. Patients with hyperdiploid karyotypes included those with 47 or more chromosomes in a clone, and patients with hypodiploid karyotypes had 45 or fewer chromosomes. Patients with insufficient metaphases included those with 10 or fewer metaphases who did not have definite, well-known abnormalities. Abnormalities of known significance (eg, Ph chromosome, t(4;11), t(1;19), and t(8;14) translocations) were included in the appropriate chromosomal category, if they were identified in at least two metaphases in cytogenetic analysis. CSF studies to document leukemic involvement were done on day 2 of the first course of treatment before the first intrathecal (IT) prophylaxis. Other studies were included as indicated by patient and disease status.

Mature B-cell ALL was diagnosed when one of the following criteria was met: L3 morphology by the French-American-British classification[49]; characteristic Burkitt chromosomal translocations including t(8;14), t(8;2), and t(8;22); or 20% or more surface immunoglobulin–positive blasts with light-chain kappa or lambda clonality.

Immunophenotyping was as follows: mature B cell, as just described; T-cell ALL, with two or more of T-cell markers (CD1 through CD8); precursor B-ALL, with CD19- or CD20-positive blasts; and CALLA-positive ALL, with CD10-positive blasts. Patients with multiple lineage-marker positivity were categorized as such (eg, T + CALLA, precursor B + T + CALLA, or precursor B + T). Myeloid-marker positivity required the presence of CD13-, CD14-, CD15-, or CD33-positive blasts. Marker positivity required the presence on 20% or more blasts.[53]

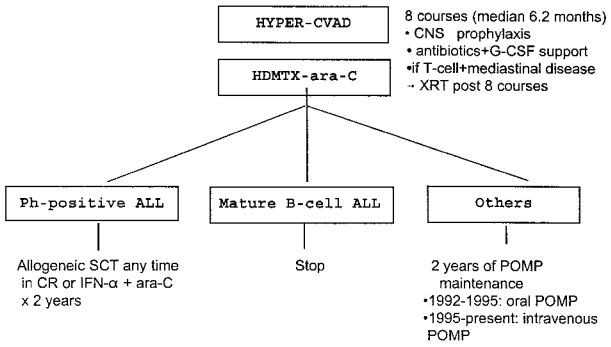

Fig 1. Simplified schema of the Hyper-CVAD program. IFN-α, interferon alfa; XRT, radiation therapy.

Eleven patients had peroxidase-negative, terminal deoxynucleotidyl transferase–positive ALL, with mostly lymphoid-negative markers (≤ one positive CD1 to CD8; CD10, CD19, and CD20 negative). Ten were Dr-positive and two were myeloid marker–positive. Other positive markers were CD4 (two patients, both myeloid negative); CD4 and CD25 (two patients); CD4, CD25, and CD38 (one patient); CD5 and CD38 (one patient); CD7 (one patient); and CD7, CD38, and CD56 (one patient, myeloid negative). These patients were in the "null"-cell category. Seven patients (64%) achieved CR; their estimated 5-year survival rate was 30%. Because they had been entered onto the study and their classification was later considered ambiguous (the disease of some of these patients was reclassified as French-American-British–M0), their data were still included in the analysis.

Therapy

The regimen consisted of two phases: a dose-intensive phase and a maintenance phase (Fig 1).

Dose-intensive phase. The dose-intensive phase consisted of eight cycles of dose-intensive therapy courses of Hyper-CVAD therapy alternating with high-dose MTX and ara-C (HD MTX–ara-C) therapy, as follows:

Hyper-CVAD: Cyclophosphamide 300 mg/m^2 intravenously (IV) over 3 hours every 12 hours for six doses on days 1 through 3, with mesna at the same total dose as cyclophosphamide but given by continuous infusion starting with cyclophosphamide and ending 6 hours after the last dose; vincristine 2 mg IV days 4 and 11; doxorubicin 50 mg/m^2 IV day 4; and dexamethasone 40 mg daily on days 1 through 4 and 11 through 14.[54]

HD MTX–ara-C: MTX 200 mg/m^2 IV over 2 hours followed by 800 mg/m^2 IV over 24 hours on day 1; citrovorum factor rescue starting 24 hours after completion of MTX infusion at 15 mg every 6 hours × 8, and increased to 50 mg every 6 hours if MTX levels were more than 20 μmol/L at the end of the infusion, more than 1 μmol/L 24 hours later, or more than 0.1 μmol/L 48 hours after the end of MTX infusion, until levels were lower than 0.1 μM; ara-C 3 g/m^2 over 2 hours every 12 hours × 4 on days 2 and 3; and methylprednisolone 50 mg IV twice daily on days 1 through 3.

CNS prophylaxis: Patients were categorized according to their expected risk of CNS disease, based on a previous multivariate analysis for prognostic factors for CNS leukemia.[55,56] Patients were considered at high risk for CNS disease if the lactate dehydrogenase level was

greater than 600 U/L (normal laboratory reference level, 25 to 225 U/L) or the proliferative index (% $S+G_2M$) was 14% or more, at low risk if neither was elevated, or at unknown risk if the measurements were not available.[55,56] Patients with mature B-cell ALL were included in the CNS high-risk category. CNS prophylaxis was given with MTX 12 mg IT on day 2 and ara-C 100 mg IT on day 8 of each cycle for 16 IT treatments in high-risk patients, four IT treatments in low-risk patients, and eight IT treatments in unknown-risk patients. Patients at low or unknown risk for CNS disease received their four or eight IT treatments on days 2 and 8 of the first two or four cycles of therapy.

Patients with CNS disease at the time of diagnosis received IT therapy twice weekly until CSF study findings were negative and then according to the schedule of the protocol. CNS disease at the time of diagnosis was considered present when there was neurologic involvement or when CSF studies showed five or more leukemic blasts per microliter of CSF fluid, without contamination of the sample with peripheral blood. Patients with cranial–nerve root involvement received 24 to 30 Gy of radiation in 10 to 12 fractions, directed to the base of the skull or to the whole brain.

Antibiotic prophylaxis: Empiric antibiotic prophylaxis was given during the dose-intensive (induction-consolidation) phase as follows: ciprofloxacin 500 mg orally twice daily or levofloxacin 500 mg daily; fluconazole 200 mg orally daily; and acyclovir 200 mg orally twice daily or valacyclovir 500 mg orally daily.

Supportive care with G-CSF: G-CSF 10 μg/kg daily was given in two divided doses starting 24 hours after the end of chemotherapy (ie, on day 5 of Hyper-CVAD therapy and day 4 of HD MTX–ara-C therapy).

Course timing and dose modifications: Subsequent courses of chemotherapy were given as soon as the WBC count was more than 3×10^9/L and the platelet count was more than 60×10^9/L. G-CSF therapy was not interrupted if platelet recovery was delayed, unless the WBC count was greater than 30×10^9/L.

The vincristine dose was reduced to 1 mg if the bilirubin level was more than 2 mg/100 mL. The doxorubicin dose was reduced by 25% if the bilirubin level was 2 to 3 mg/100 mL, by 50% if it was 3 to 4 mg/100 mL, and by 75% if it was more than 4 mg/100 mL.

The MTX dose was reduced by 25% when creatinine levels were 1.5 to 2.0 mg/100 mL and by 50% when levels were higher. The ara-C dose was reduced to 1 g/m^2 in patients 60 years or older, if the creatinine level was greater than 2.0 mg/100 mL, or if the MTX level at the end of the MTX infusion (0 hours after completion of MTX therapy) was 20 μmol/L or more.

Subsequent Hyper-CVAD treatment courses (courses 3, 5, and 7) did not usually require dose reductions for serious toxicities. With HD MTX–ara-C treatment courses, serious toxicities (usually grade 3 to 4 myelosuppression–associated complications other than neutropenia or thrombocytopenia) required subsequent dose reductions of 25% to 33%: the MTX dose to 750 mg/m^2 and then to 500 and 250 mg/m^2; and the ara-C dose to 2 g/m^2 and then to 1.5 and 1 g/m^2.

Maintenance phase. Patients with mature B-cell ALL received no maintenance therapy. Patients with Ph-positive ALL who were candidates for allogeneic SCT and had a matched related (or one antigen mismatch) donor, or who had a matched unrelated donor, underwent allogeneic SCT as soon as possible in CR (without continuing the intensive phase). Otherwise, maintenance consisted of interferon alfa 5 MU/m^2 subcutaneously daily and ara-C 10 mg subcutaneously daily for 2 years.

All other patients received maintenance therapy with mercaptopurine (6-MP), MTX, vincristine, and prednisone (POMP) for 2 years. Between 1992 and 1995, oral POMP was given: 6-MP 50 mg orally 3 times daily (on an empty stomach), MTX 20 mg/m^2 orally weekly, vincristine 2 mg IV monthly, and prednisone 200 mg daily $\times$ 5 monthly with vincristine. From 1995 on, IV POMP was administered: 6-MP 1 g/m^2 IV over 1 hour daily $\times$ 5 every month, MTX 10 mg/m^2 IV over 1 hour daily $\times$ 5 every month, and vincristine and prednisone monthly as just described. The 6-MP and MTX doses were reduced by 25% (to 750 mg/m^2 and 7.5 mg/m^2, respectively) in cases of moderate toxicity and by 50% (to 500 mg/m^2 and 5 mg/m^2, respectively) in cases of severe toxicity. Mucositis and hepatic dysfunctions were more related to MTX therapy, and the MTX dose was generally reduced selectively before 6-MP dose reductions were considered.

Antibiotic prophylaxis given during the maintenance phase consisted of trimethoprim-sulfamethoxazole twice daily on weekends, and acyclovir 200 mg or valacyclovir 500 mg daily or three times weekly, for the first 6 months, to reduce the probability of pneumocystis infection, herpes zoster, or varicella.

Response and Toxicity Criteria and Statistical Methods

Response criteria were previously described.[3] Complete response required normalization of peripheral counts (granulocyte count greater than 10^9/L and no abnormal peripheral blasts) with no more than 5% marrow blasts. Consolidation courses were started when the platelet count reached 60×10^9/L (if other complete response criteria were met). All such patients were in marrow CR and subsequently showed platelet recovery of more than 100×10^9/L. Bone marrow aspirations for follow-up and to confirm CR were performed on days 14 and 21 of the induction cycle, then every 3 to 7 days as indicated until CR, then every 2 to 4 months during CR in the first 2 years, and then as indicated. Toxicity criteria were according to the National Cancer Institute recommendations.[57]

Survival was calculated from the date of initiation of therapy, and CR duration was calculated from the date of achievement of CR until evidence of leukemia recurrence (10% or more lymphoblasts in marrow). Death in CR was censored at the time of death for CR duration curves. Survival and CR duration distributions were estimated using the Kaplan-Meier method and compared using the log-rank test.[58,59] Differences in response rates were analyzed using a χ^2 test. Data from patients undergoing allogeneic SCT were not censored at the time of transplantation and were evaluated according to eventual outcome.

A proportional hazards model[60] was used to evaluate whether a previous risk model for CR duration could be improved on with additional pretreatment information. Proportional hazards assumptions were verified[61] and the functional forms of associations between patient characteristics and CR duration were investigated by inspection of residuals computed in the fitting process.[62]

Hyper-CVAD versus VAD. To evaluate the potential benefit of Hyper-CVAD therapy, the results were compared with results achieved with three previous VAD regimens used between 1982 and 1991 in patients with newly diagnosed adult ALL.[3] Entry criteria were similar during the two study periods.

RESULTS

Study Group

Characteristics of the 204 patients treated are summarized in Table 1. Median age was 39.5 years (mean, 42 years; range, 16 to 79 years); 75 (37%) were 50 years or older and 44 (22%) were 60 years or older. A total of 71 patients

Table 1. Characteristics of the Study Group (204 patients)

Characteristic	No.	%
Age*		
< 30 years	65	32
30-50 years	64	31
50-59 years	31	15
≥ 60 years	44	22
Performance score 3-4 (Zubrod scale)	15	7
Splenomegaly	51	25
Hepatomegaly	32	16
Lymphadenopathy	65	32
CNS disease at diagnosis	14	7
Mediastinal mass	11	5
WBC count		
$< 5 \times 10^9$/L	71	35
5-30 $\times 10^9$/L	80	39
$> 30 \times 10^9$/L	53	26
Platelet count $< 100 \times 10^9$/L	151	74
Hemoglobin level < 10 g/dL	132	69
Lactic dehydrogenase level > 600 U/L	104	59
Alkaline phosphatase level ≥ 80 U/L	146	72
Creatinine level ≥ 1.3 mg/100 mL	33	16
Bilirubin level ≥ 1.3 mg/100 mL	26	13
Karyotype		
Diploid	46	22
Ph-positive	32	16
t(8;14), t(8;2), t(8;22)	9	4
6q−;14q+	12	6
Insufficient metaphases	46	22
Hyperdiploid	9	4
Hypodiploid	11	5
Other†	39	19
FAB classification		
L1	51	25
L2	93	45
L3	11	5
Not classified/mixed	42/4	23
Immunophenotype		
Mature B	18	9
T	18	9
T-CALLA	6	3
Precursor B	28	14
T-precursor B–CALLA	12	6
CALLA	107	53
Null	11	5
Myeloid markers		
Positive	97	54
Negative	82	46
Not performed/unknown	4/21	
Systemic risk at CR (MDACC)		
Low	48	26
Intermediate	87	47
High	50	27
Hoelzer risk at CR		
Low	37	22
High	134	78
Risk for CNS disease		
High	113	55
Low	53	26
Unknown	38	19

Abbreviation: FAB, French-American-British; MDACC, M.D. Anderson Cancer Center.

*Median age, 39.5 years.

†Including two patients with t(4;11) and five with t(1;19).

(35%) were female. Splenomegaly was present in 25%, hepatomegaly in 16%, and lymphadenopathy in 32%. Median WBC count was 7.7 $\times 10^9$/L, median hemoglobin level was 9.0 g/dL, and median platelet count was 49 $\times 10^9$/L. CNS leukemic involvement was present in 14 patients (7%); 18 (9%) had mature B-cell ALL, and 16% (20% of those with assessable karyotypes) had Ph-positive ALL. Seventy-four percent of patients were at high risk for systemic relapse, defined previously,[3] and 113 of 166 assessable patients (68%) were at high risk for CNS relapse. Patients were considered to be at intermediate-high risk of systemic relapse if they had Ph-positive disease, B-cell ALL, CNS leukemia, or WBC counts of more than 5 $\times 10^9$/L or required more than one course to achieve CR.[3] High-risk patients included those with Ph-positive ALL, B-cell ALL, or CNS leukemia; intermediate-risk patients had leukocytosis of 5 $\times 10^9$/L or required more than one course to achieve CR.[3] By Hoelzer's model, patients are at high risk for relapse if they are older than 35 years, have WBC counts of ≥ 30 $\times 10^9$/L, or require more than 4 weeks to achieve CR.[6]

Treatment Results

One hundred eight-five (91%; 95% confidence interval [CI], 86% to 94%) of 204 patients achieved CR, 12 (6%) died during remission induction, and seven (3%) had resistant disease. The primary causes of deaths during induction therapy were fungal infections (four patients: aspergillosis in three and candida infection in one) and bacterial infections (eight patients: sepsis with or without pneumonia in four and other infections in four; three of the eight had significant hemorrhagic components in major organs [CNS, lungs] at the time of death). Multiple organ failures (primarily renal and hepatic) were present by the time of death in eight patients. The median time to achieve CR was 21 days. One hundred fifty-one achieved CR after one course, whereas 34 required two or more courses. The median time to starting a second course was 21 days.

After a median follow-up of 40 months (range, 4+ to 83+ months),[63] 96 patients remained alive, 84 of them in first CR. One hundred eight patients died: 12 during induction therapy, 85 after leukemia recurrence, and 11 from treatment complications (all infections) while in CR (one after allogeneic SCT). Twelve patients who relapsed were still alive at the time of writing: seven with leukemia and five in subsequent remissions, two of them after allogeneic SCT (one received a matched related-donor transplant, the other a matched unrelated-donor transplant).

The estimated median survival time of patients on the study was 35 months (95% CI, 24 to 48 months), with a 5-year estimated survival rate of 39% (95% CI, 31% to

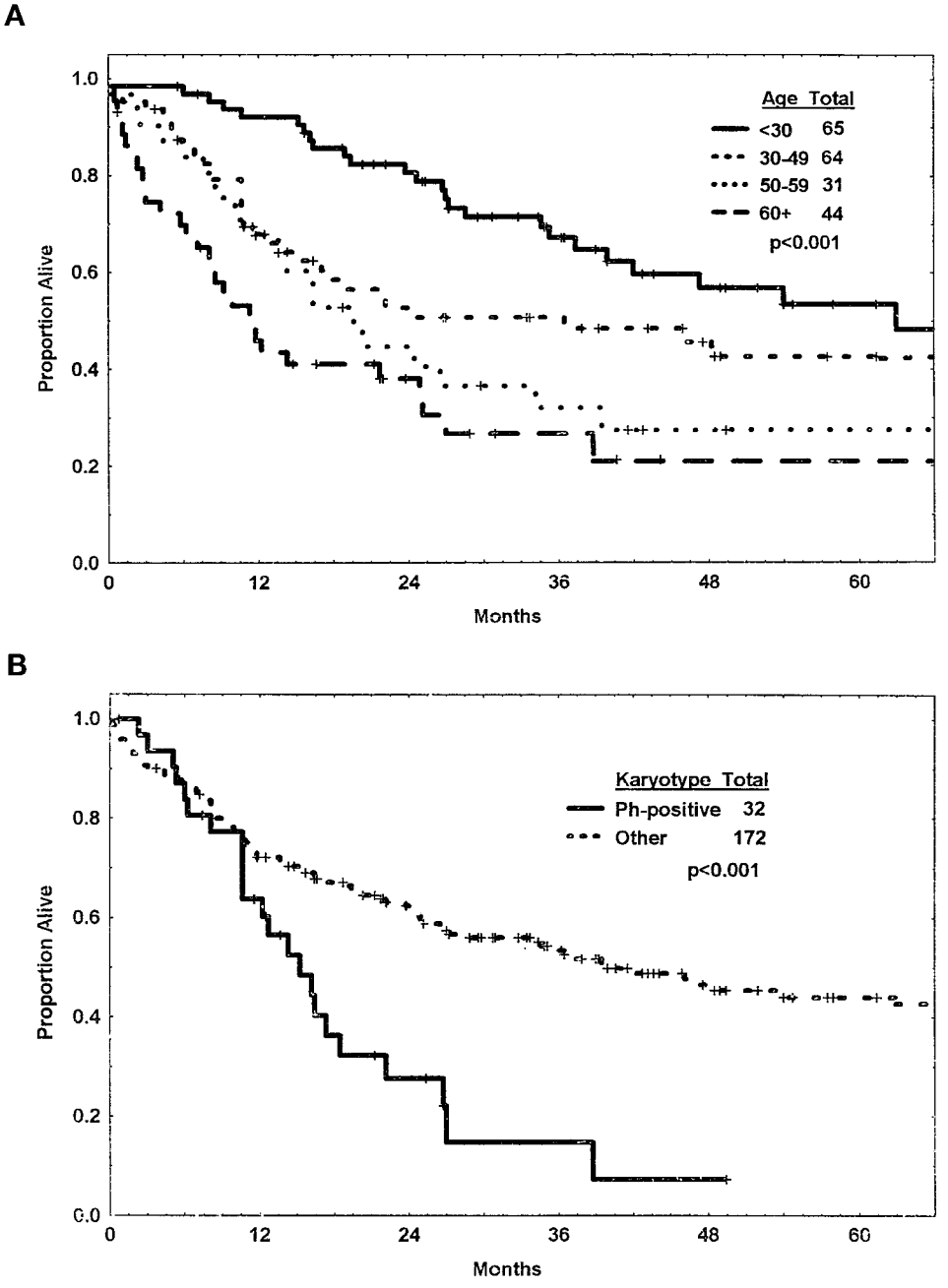

Fig 2. Survival of 204 patients receiving Hyper-CVAD therapy, by age (A) and Ph-positive status (B).

48%). Among patients achieving CR, the estimated median CR duration was 33 months (95% CI, 21 to 40 months) and the 5-year estimated CR rate was 36% (Figs 2-4).

Response by pretreatment characteristic is summarized in Table 2. The CR rate for patients younger than 30 years was 98%, similar to that for patients with childhood ALL. However, patients 60 years or older had a lower CR rate (79%), mostly due to a higher incidence of induction-therapy mortality: seven of 44 older patients died during remission induction (16% mortality), making up most of the remission-induction deaths (seven of 12 total deaths, or 58%). Neither leukocytosis nor karyotypic abnormality was associated with differences in CR rates. Patients with WBC counts of $\geq 50 \times 10^9$/L had a CR rate of 93%, whereas those with Ph-positive disease had a CR rate of 91%. Sixteen patients had leukocytosis of $\geq 100 \times 10^9$/L,

Table 2. Response and Survival, by Pretreatment Characteristic

Characteristic	No. of CRs/Total	%	*P*	5-Year Survival Rate (%)	*P*
Age					
≤ 30 years	64/65	98	.01	54	< .01
30-49 years	57/64	89		42	
50-59 years	29/31	93		29	
≥ 60 years	35/44	79		17	
Performance score					
0-1	132/139	95		45	< .01
2	44/50	88	< .01	32	
3-4	9/15	60		< 12	
Hepatomegaly					
No	160/172	93	.01	41	.04
Yes	25/32	78		29	
WBC count					
≤ 5×10^9/L	64/71	90	.54	36	.58
5.1-30 $\times 10^9$/L	71/80	89		45	
> 30×10^9/L	50/63	91		32	
Platelet count					
< 20×10^9/L	15/19	79		9	< .001
20-49 $\times 10^9$/L	74/183	89	.08	29	
50-99 $\times 10^9$/L	44/49	90		50	
≥ 100×10^9/L	52/53	98		54	
Albumin level					
< 3 mg/100 mL	28/37	76	< .01	34	.01
≥ 3 mg/100 mL	157/167	94		40	
Bilirubin level					
< 1.3 mg/100 mL	164/177	93	.01	45	.03
≥ 1.3 mg/100 mL	20/26	77		10	
FAB classification					
L1	51/54	94		58	
L2	86/93	92	.10	26	.06
L3	8/11	73		33	
Other	40/46	87		38	
Immunophenotype					
Mature B	16/18	89	.03	29	.46
T	24/24	100		43	
Precursor-B	25/28	89		31	
CALLA	99/107	92		38	
Null	7/11	64		30	
T–precursor	9/12	75		27	
B–CALLA					
Karyotype					
Ph-positive	29/32	91	.9	7	< .01
Other	156/172	91		45	
Myeloid markers					
Positive	86/97	89	.36	35	.58
Negative	76/82	93		45	(+ vs −)
Unknown	23/25	92		38	

including 12 patients with non T-cell ALL: 15 (94%) achieved CR. Eleven patients had null-cell immunophenotypes, and only 7(64%) achieved CR.

There were no marked differences in CR rates by sex; presence of splenomegaly, adenopathy, mediastinal disease, or CNS disease; degree of anemia; presence of peripheral blasts; or presence of elevated creatinine, lactate dehydrogenase, alkaline phosphatase, or beta-2-microglobulin levels (data not shown). However, patients with poor performance status, hypoalbuminemia, or hepatomegaly had lower CR rates (60% to 78%), mostly because of high induction-therapy mortality rates (poor performance status, six deaths among 15 patients [40%]; hypoalbuminemia, nine deaths among 37 patients [24%]; hepatomegaly, five

deaths among 32 patients [16%]). In correlation with the adverse effect of hepatomegaly, hyperbilirubinemia was also associated with a lower CR rate (77%) because of higher mortality (five deaths among 26 patients [19%]). Among the 44 patients 60 years or older, eight (18% *v* 4% for others, $P < .01$) had a poor performance status (score of 3 to 4); 18 (41% *v* 12%, $P < .01$) had hypoalbuminemia; eight (18% *v* 15%, $P = .61$) had hepatomegaly; and six (14% *v* 12%, $P = .8$) had hyperbilirubinemia. Among the 12 patients who experienced induction-therapy failure, seven (58%) were 60 years or older, six (50%) had a poor performance status (score of 3 to 4), nine (75%) had albumin levels of less than 3 mg/100 mL, five (42%) had elevated bilirubin levels; and five (42%) had hepatomegaly.

Survival

Survival rate by age group is plotted in Fig 2A ($P < .001$). Patients less than 30 years old had an estimated 5-year survival rate of 54%, and, in relation to SCT results, those less than 50 years old had an estimated 5-year survival rate of 48%. Patients 60 years or older had an estimated 3-year survival rate of 25%. Patients with Ph-positive ALL had poor survival (Fig 2B) ($P < .01$). There was a significant trend toward association of lower platelet counts with shorter survival (Table 2). With this dose-intensive regimen, there was only a small trend toward association of degree of leukocytosis with survival, a phenomenon not observed in previous studies of childhood or adult ALL. The 16 patients with WBC counts of $\geq 100 \times 10^9$/L had a 3-year survival rate of 37%, compared with 50% for the others ($P = .20$); the subset of 12 patients with non–T-cell ALL and this degree of leukocytosis had a 3-year survival rate of 33% ($P = .30$). Consequent to the worse CR rate, survival (but not CR duration) tended to be significantly worse with poor performance (score of 3 to 4) ($P < .01$), hepatomegaly ($P = .04$), hyperbilirubinemia ($P = .03$), and hypoalbuminemia ($P = .01$). This was also noted with elevated serum beta-2-microglobulin levels ($P < .01$), although levels were unknown in 47 cases. There was no evidence of important association between outcome and sex; degree of anemia; presence of peripheral blasts or percentage of marrow blasts; presence of a mediastinal mass, splenomegaly, CNS disease, or lymphadenopathy; or creatinine or lactate dehydrogenase levels.

Comparison of Hyper-CVAD and VAD Regimens

Characteristics of 222 patients in previous VAD trials were similar to those of patients treated with Hyper-CVAD: median age of 34 years (Hyper-CVAD patients, 39.5 years), median WBC count of 8.5×10^9/L (*v* 7.7×10^9/L), performance score of 3 or 4 in 7% (*v* 7%), and Ph-positive disease in 14% (*v* 16%). Seventy-five percent of patients (164 of 218 assessable patients) treated with VAD achieved CR, compared with 91% of those treated with Hyper-CVAD ($P < .01$). The rate of induction-therapy death was similar with the Hyper-CVAD and VAD regimens (6% *v* 5%), but the rate of resistant disease (evaluations made after two courses) was significantly less with Hyper-CVAD therapy (3% *v* 20%, $P < .01$). Similarly, early parameters of tumor-burden reduction, including achievement of CR after one course of therapy (74% with Hyper-CVAD therapy and 55% with VAD therapy, $P < .01$) and of more than 5% persistent marrow blasts on day 14 of course 1 (34% *v* 48%, $P = .01$), were better with the Hyper-CVAD regimen.

Survival was significantly better with Hyper-CVAD therapy (Fig 3). Estimated 5-year survival rates were 39% with Hyper-CVAD therapy and 21% with VAD therapy ($P < .01$). Despite a CR-rate difference of 16% between the regimens, remission also tended to be longer with Hyper-CVAD therapy than with VAD therapy (Fig 4); estimated 5-year CR rates were 38% and 32%, respectively ($P = .07$).

Maintenance Therapy

To evaluate the effect of maintenance therapy with IV (n = 58) versus oral POMP (n = 60), we analyzed CR duration and survival, measured from the start of POMP maintenance therapy. The 3-year CR rates were 63% and 52% for IV and oral POMP therapy, respectively ($P = .38$), and the 3-year survival rates were 70% and 62%, respectively ($P = .62$).

Complete Response Duration and Verification of Risk Models

The estimated median duration of CR was 33 months; 84 patients remained in CR at the time of analysis, 35 longer than 3 years. CR durations for subsets of patients grouped by characteristics are summarized in Table 3. There were marked trends toward shorter remissions among older patients, those with poor performance status or low initial platelet counts, those with Ph-positive disease, and those who required more than one course of therapy to achieve CR. Leukocytosis was associated with a trend toward worse CR duration ($P = .11$, Table 3). The 15 patients with leukocytosis of $\geq 100 \times 10^9$/L had a 3-year CR rate of 35%, compared with 52% for the others ($P = .06$). Among the 11 patients with non–T-cell ALL and WBCs of $\geq 100 \times 10^9$/L, the 3-year CR rate was 27%, compared with 47% for the others ($P = .16$). Two algorithms for assigning risk of

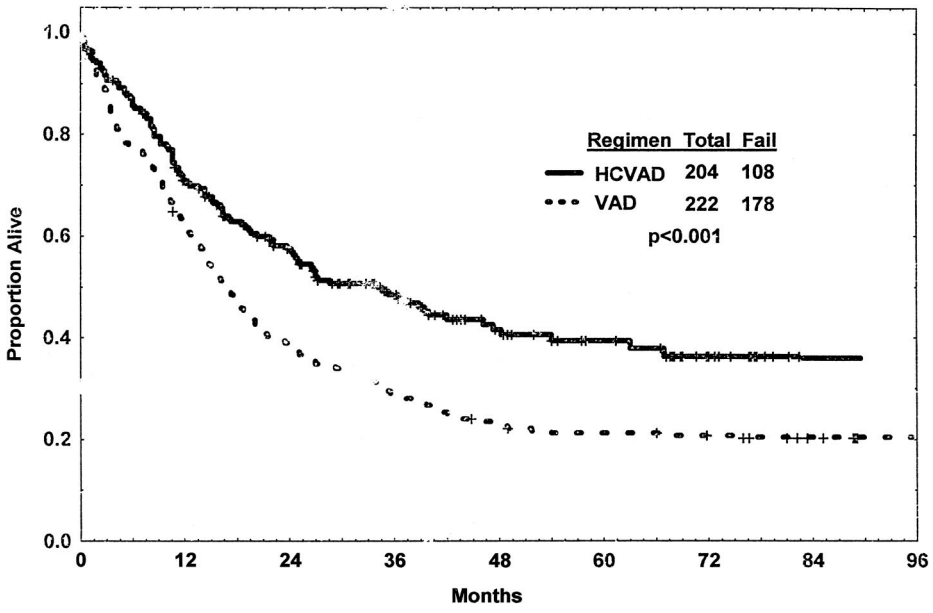

Fig 3. Survival with Hyper-CVAD versus VAD therapy.

relapse (Kantarjian et al[3] and Hoelzer et al[6]) were applied to the group, and duration of CR was compared among risk categories (Table 3). There were significant trends toward shorter CRs among patients classified as being at higher risk by either model.

In an attempt to improve the risk-classification scheme, the functional form of the associations of age, platelet count, and WBC count with CR duration was further investigated by inspection of residuals computed through the fit of a proportional hazards model.[62] Each factor was fitted individually, using log transformations of platelet and WBC counts, and residuals were plotted. These suggested a decreasing risk of relapse with increasing platelet count throughout its observed range. For WBC count, the risk of relapse increased substantially only when WBC values reached 20×10^9/L or greater. For patients younger than 35 years, there was no apparent difference in outcome, but for older patients, increasing age was associated with increased

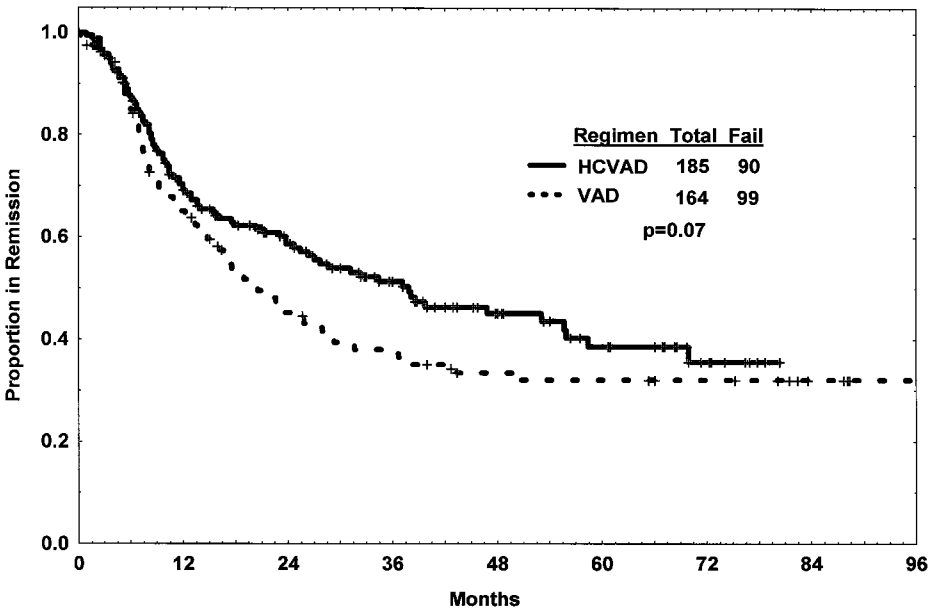

Fig 4. CR duration with Hyper-CVAD versus VAD therapy.

Table 3. Complete Remission Duration by Patient Characteristic

Characteristic	No.	CR Duration (years) 3	5	P
All patients	185	50	38	
Age				
< 30 years	64	52	38*	<.01
30-49 years	57	55	51*	
50-59 years	29	34	17*	
≥ 60 years	35	36*	18*	
Performance score				
0-1	132	52	35	.06
2-4	53	39	39*	
WBC count				
≤ 5×10^9/L	66	49	36*	.05
5.1-30 $\times 10^9$/L	59	58	47*	
> 30 $\times 10^9$/L	50	31*	31*	
Platelet count				
< 20 $\times 10^9$/L	15	47*	0	<.01
20-49 $\times 10^9$/L	74	39	34*	
50-99 $\times 10^9$/L	44	58	33*	
≥ 100 $\times 10^9$/L	52	55	55*	
Immunophenotype				
Mature B	16	33*	33*	.25
T	24	53*	53*	
Precursor-B	25	56*	56*	
CALLA	99	41	31*	
Karyotype				
Ph-positive	29	15*	—	<.01
Other	156	54	42	
No. of courses to CR				
1	151	55	46	<.01
> 1	34	24	13*	
Systemic risk group (MDACC)				
Low	48	55	48*	.01
Intermediate	87	47	33	
High	50	32	22*	
Hoelzer risk group				
Low	37	48	44*	.05
High	134	46	35*	
Augmented model in test group				
Low	31	68	68*	<.01
Intermediate	32	48	14*	
High	28	23*	11*	

*Estimates based on fewer than 10 patients.

risk of relapse and three age groups were subsequently considered: less than 35, 35 to 54, and ≥ 55 years.

A random subset of approximately one half of the patients was selected and proportional hazards modeling[60] was used to develop a risk model. A model with terms for risk group,[3] age, platelet count, and WBC count was fitted in the subset and applied to the remaining patients, who served as a test group. The results are summarized in Table 3. Although there was a clear separation of the prognostic groups, the distinction in the test group was not clearly superior to existing models.[3,6]

CNS Relapses

Fourteen patients presented with CNS disease: 12 achieved both systemic remission and CNS remission, but seven relapsed later with systemic disease only (five patients) or with CNS disease (two patients).

Among 190 patients without initial CNS leukemia, five (3%) developed later isolated CNS disease before systemic relapse (one patient) or concomitant with marrow relapse (four patients). These included three (6%) of 51 patients at low risk for CNS disease, two (2%) of 104

patients at high risk, and none of 35 patients at unknown risk.

T-Cell Disease

All 24 patients with T-cell ALL, including those with T + CALLA–positive ALL (n = 6), achieved CR. Their 5-year CR rate was 47%, compared with 33% for the other patients ($P = .13$), and their 5-year survival rate was 43%, compared with 37% ($P = .17$).

Eight patients (33%) had T-cell ALL and mediastinal disease. One patient died in CR on course 8 of HD MTX–ara-C therapy without mediastinal disease. Two additional patients relapsed before the time of mediastinal irradiation, one with mediastinal and marrow relapse, the other with marrow and cervical lymph node relapse.

Of the five remaining patients, three underwent mediastinal irradiation. None of the five had mediastinal relapse, but two had systemic relapse (one of two who did not undergo irradiation, and one of three who did). Mediastinal irradiation was performed for a total of 39.6 Gy, delivered in 22 fractions over 4.5 weeks (5 days on, 2 days off).

Ph-Positive Disease and Other Chromosomal Abnormalities

Among 32 patients with Ph-positive ALL who were treated, 29 (91%) achieved CR and three had resistant disease. Their 5-year survival rate was 7%. Only six patients (21%) were eligible for and underwent allogeneic SCT. Their ages were 46, 38, 34, 31, 24 and 16 years. The median time to allogeneic SCT was 3.5 months. Two relapsed 5 and 7 months after allogeneic SCT and died 8 and 25 months after SCT, one died in CR 7 months after SCT, and the other three were alive in CR 6+, 19+, and 24+ months after SCT.

Among the remaining 23 patients who achieved CR, two died in CR during consolidation, six relapsed during consolidation, nine relapsed during maintenance therapy (seven receiving interferon alfa therapy). Thus, only six patients remained in CR at the time of writing (two were undergoing consolidation, two were receiving POMP maintenance therapy, and two had finished maintenance therapy).

In this study, two patients (1%) had t(4;11)(q21;q23) translocations. These patients achieved CR but relapsed at 11 and 16 months and died at 14 and 20 months. Five patients (2%) had t(1;19)(q23;p13) translocations. All five achieved CR; one patient died in CR at 3 months while receiving consolidation therapy, two patients relapsed at 10 and 20 months and died at 24 and 37 months, and two patients were still alive in CR at 48+ and 77+ months.

Side Effects

With induction chemotherapy (first course of Hyper-CVAD therapy), myelosuppression-associated complications were the most common side effects. The median time to recovery of granulocytes to more than 10^9/L was 18 days, and to platelets more than 100×10^9/L 21 days. Hospitalization was required in 63% of patients, some with several of the following problems: documented infections (sepsis 15%, pneumonia 22%, fungal infection 4%, other minor infections 14%); fever of unknown origin 45%. Other significant side effects included neurotoxicity, mostly steroid-related (6%), moderate-severe mucositis (6%), moderate-severe diarrhea (3%), ileus (2%), and disseminated intravascular coagulopathy requiring therapy (2%).

Side effects during Hyper-CVAD consolidation courses were minimal. The dose-intensity delivery was 100%. Myelosuppression-associated side effects included documented infections (10%: sepsis, 3%; pneumonia, 2%; minor infections, 5%) and fever of unknown origin (8%). Hospitalization was required in 18% of courses. Other significant side effects included neurotoxicity (8%), mostly steroid-associated mood changes or depression, mucositis and diarrhea (2%), cardiac complications (1%), and G-CSF therapy–associated bone aches (5%). The median time to recovery of counts and delivery of the next course was 20 days.

With HD MTX–ara-C therapy, myelosuppression-associated complications were more frequent. These included sepsis (11%), pneumonia (5%), fungal infections (two patients, < 1%), minor infections (7%), and fever of unknown origin (23%). Other side effects were renal and hepatic toxicities (2%), neurotoxicity (5%), skin rashes (5%), rash and desquamation of palms and feet (3%), mucositis (5%), diarrhea (1%), ara-C therapy–associated fever (6%), and G-CSF therapy–associated bone aches (1%). Reversible renal failure (creatinine levels of ≥ 3 mg/100 mL) from MTX therapy occurred in three patients, and high-dose ara-C therapy–associated, severe reversible neurotoxicity (ataxia, cerebellar toxicity) occurred in four patients. Hospitalization for side effects was needed in 42% of courses. Although the median dose-intensity delivery was 100%, MTX dose reductions were required down to 75% in 18%, to 50% in 15%, and to 25% in 3%. Dose reductions of ara-C were required in 35% of courses, mostly for patients more than 60 years old (1 g/m^2; 19% of courses). The median time to recovery and delivery of the next course was 22 days.

The median time to delivery of all eight courses was 6.2 months. Maintenance therapy with POMP was well tolerated. Myelosuppression-associated complications were sep-

sis (5%), pneumonia (7%), minor infections (8%), and fever of unknown origin (7%). Other side effects were moderate hepatotoxicity (10%) and mucositis or diarrhea (10%).

Unusual side effects included herpes zoster or varicella (8%), cytomegalovirus infection in 5%, and pneumocystis infection in 1%.

DISCUSSION

The results achieved with Hyper-CVAD treatment were encouraging. The overall CR rate was 91%, and induction-therapy mortality was low (6%). The estimated 5-year CR rate was 38% and the estimated 5-year survival rate was 39%. These results were achieved despite broad entrance criteria (no exclusions by age, performance status, organ dysfunction, or infection status at the time of diagnosis). Median age was 39.5 years, about 10 years higher than that of subjects in published studies of adult ALL, and 22% of patients were 60 years or older. Outcome was significantly superior with Hyper-CVAD therapy compared with the VAD regimens, in terms of both CR rate and long-term prognosis.

Analysis of prognostic factors suggested that some previously well-established poor prognostic factors such as the degree of leukocytosis were less important with this dose-intensive regimen. This is in line with observations in other tumors, in which prognostic factors are treatment dependent and in which improved therapy has either eliminated, modified, or minimized the effect of the pretreatment variable (eg, testicular cancer or hairy-cell leukemia). On the other hand, although the CR rate was high in Ph-positive ALL, this resistant form of ALL remained resistant to dose-intensive therapy. This is in keeping with recent results with marrow ablative therapy in Ph-positive ALL that indicated that the cure rate remains as low as 20%. In accordance with our previous experience[53] and with other reports,[44,64,65] the presence of myeloid markers (in approximately 50% of cases in this series) was not an indicator of unfavorable prognosis, and myeloid markers should not be considered markers of unfavorable mixed-lineage disease.

The application of prognostic models[3,6] to the present study group showed a good separation of different risk groups (Table 3). Our attempts to improve on an earlier prognostic model suggested that minor improvements may be realized by additional considerations of conventional risk factors, though major improvements await further discoveries regarding underlying disease molecular pathophysiology and how to measure it.

The dose-intensity of the regimen was predictably associated with a high incidence of myelosuppression-related complications such as infections, particularly with the HD MTX–ara-C therapy courses. However, induction-therapy mortality was only 6%, and only 11 patients (5%) died during the intensive or maintenance phase. The benefit of growth-factor support has been confirmed in several series, but the optimal dose schedule of G-CSF needs further elucidation. Of concern was the occurrence of several infections associated with immunosuppression, including pneumocystis, cytomegalovirus, and herpes infections. Their incidence was similar to that seen with autologous marrow ablative therapy (approximately 10%). It suggests that dose-intensive immunosuppressive therapy cannot be further escalated without possible serious deleterious effects, which may counterbalance the dose-intensive treatment benefits.

CNS prophylactic irradiation was not incorporated in our treatment program; rather, reliance was placed on IT therapy and high-dose systemic therapy. The low incidence of CNS relapse suggests that the efficacy of IT therapy plus high-dose systemic therapy is similar to that of craniospinal irradiation. This is in line with the results in childhood ALL,[66] which will alleviate the long-term neurotoxicities attributed to radiation therapy. Given that none of the 35 patients with unknown risk for CNS disease had CNS relapse, eight IT treatments may be sufficient CNS prophylaxis, except in mature B-cell ALL or when CNS disease is present at the time of diagnosis.

A significant proportion of patients receiving Hyper-CVAD therapy still die from disease progression. Several approaches may improve prognosis, including dose-intensive anthracycline induction therapy, as proposed by Todeschini et al[34,35]; treatment with dose-intensive asparaginase[10,35] or the new polyethylene glycol formulation of asparaginase (PEG-asparaginase)[67-69]; use of new agents with selective or targeted effects such as Compound 506U,[70] monoclonal antibodies, or tyrosine kinase inhibitors[71,72]; and immunomodulatory approaches.

The omission of asparaginase in the Hyper-CVAD regimen and its relation to T-cell–ALL prognosis should be considered. In previous studies, the improved T-cell–ALL outcome was attributed to cyclophosphamide and ara-C pulses.[6,10] The Hyper-CVAD regimen includes both fractionated cyclophosphamide and ara-C. The 5-year survival rate in T-cell ALL was 43% and the 5-year CR rate was 47%. In the Cancer and Leukemia Group B (CALGB) report,[10] the 3-year survival rate was estimated to be 69% in T-cell ALL, compared with 63% in our study. Whether any differences will emerge related to differences in diagnostic criteria, study groups, or omission of asparaginase remains to be elucidated in longer follow-up and with studies addressing the importance of asparaginase.

Recent studies with a nucleoside analog, guanosine arabinoside, and with its prodrug form, Compound 506, have

shown major activity in childhood and adult T-cell ALL.[70] Incorporating these agents into T-cell ALL maintenance therapy, and monitoring for minimal residual disease, may result in further improvement in the cure rates and in shortening the duration of maintenance therapy. The value of mediastinal radiation therapy in patients with T-cell ALL and mediastinal disease remains controversial. Although some of our patients received radiation therapy on the basis of the results of Hoelzer,[8] results of the CALGB analysis[10] suggest this may not be necessary. Twenty-one patients with lymphoblastic lymphoma (two thirds with mediastinal disease) without marrow involvement have been treated with the same Hyper-CVAD regimen at our institution: 20 (95%) have achieved CR, and the 3-year survival rate was 75%, significantly better than in T-cell ALL.[73] It is possible that lack of marrow involvement in lymphoblastic lymphoma may be associated, as in other lymphomas (eg, Burkitt's lymphoma), with better prognosis.

In childhood ALL, long-term prognosis has been associated with the total dose of 6-MP delivered and plasma or cellular levels of 6-MP and MTX.[74-76] Both agents are erratically absorbed, with absorption rates ranging from 20% to 80%. Oral 6-MP is also dose limited by hepatotoxicity. At least one study in adult ALL indicated that dose-intensive POMP therapy improves patient prognosis.[77] IV dose-intensive POMP maintenance therapy may reduce problems due to noncompliance, erratic absorption, and hepatotoxicity and would allow delivery of doses of 6-MP and MTX two to five times higher, which it is to be hoped would improve long-term prognosis.[78,79] Our preliminary experience with IV POMP maintenance therapy did not demonstrate large differences compared with oral POMP therapy, although the patient subsets were small.

Although the Hyper-CVAD regimen was based on the dose-intensive short-term therapy for childhood Burkitt B-cell ALL, the results in patients with mature B-cell ALL were not as favorable as expected.[80] This may be due to the absence of any selective entrance criteria in our study, as well as the worse status of the patients with mature B-cell ALL treated with Hyper-CVAD therapy. Thomas et al[80] reported the median age of our patients with mature B-cell ALL to be 56 years, in comparison with median ages of 30 to 40 years in other programs.[21-23] More important, patients 60 years or older had a worse outcome, probably due to biologic features of the disease rather than to older age. The long-term DFS rate was more than 60% in patients younger than 60 years but only 15% in patients 60 years or older, which may constitute approximately 50% of unselected patients. In the latter group, better supportive care and combining of monoclonal antibody therapy (eg, anti-CD20) with chemotherapy may improve results.

The Hyper-CVAD regimen has also been used in patients with other lymphoproliferative disorders such as chronic lymphocytic leukemia, multiple myeloma,[81] mantle-cell lymphoma,[82] and lymphoblastic lymphoma[73] with encouraging results.

Although Hyper-CVAD therapy was superior to our previous VAD regimens, which were studied in comparable patients, characteristics of the study groups and ease and efficacy of treatment delivery must be taken into account in

Table 4. Comparison of the HYPER-CVAD Program With Established ALL Treatment Programs

Regimen	Hyper-CVAD	L2-L17M[7]	L10-M[9]	BMF[6]	CALGB[10]
No. entered/No. evaluated	204/204	199/199	182/168	384/368	214/197
Median age, years	39.5	NS	28	25	32
Age, %					
≥ 60 years	22	NS	NS	NS*	9
≥ 50 years	37	16	24	NS	NS
≥ 35 years	59	32	NS	26	NS
Performance score (Zubroad scale), %					
3-4	7	NS	NS	NS	NS
2-4	32	NS	NS	NS	16
Organ dysfunction allowed	Yes	NS	No	NS	No
Ph-positive ALL, %	16	9	NS	"Few"	22 (25/116)
T-cell ALL, %	17	15	14	22	28
WBC count $> 30 \times 10^9$/L, %	26	NS	29	36	34
CR rate, %	91	82	68	74	85
Survival rate, %					
3-year	50	43	35	43	50
5-year	39	37	28	39	42

Abbreviations: BMF, Berlin-Frankfurt-Münster; NS, not stated.

*Patients ≥ 65 years old were excluded.

making comparisons. Randomized trials are needed in which patients are accrued under similar entrance criteria and have similar treatment conditions. Because adult ALL is rare, such studies are not developed in cooperative efforts unless the investigators are convinced of the potential superiority of the proposed new regimen. Characteristics of patients receiving and results achieved with Hyper-CVAD therapy and with four established regimens (Sloan Kettering, modified L10, Berlin-Frankfurt-Münster, and CALGB) are compared in Table 4. Our study included older patients and allowed for inclusion of patients with worse organ function and poor performance status. Only 9% of patients in the CALGB study were ≥ 60 years, compared with 22% in our study; the CR rates in this subgroup were 39% and 67%, respectively. Performance scores of 2 to 4 (Zubrod scale) were present in 16% of patients in the CALGB study compared with 32% in our study. The original Berlin-Frankfurt-Münster study included younger patients (median age, 25 years [39.5 years in our study]) and patients more than 65 years old were excluded; still, the CR rate was 74% (91% in our study), and the 5-year survival rates were comparable. Importantly, 204 of a total of 208 patients referred were included in our study group (four had other active metastatic cancers); in other words, more than 98% of referred patients were included in the program. Despite published entry criteria, selection biases (older age, poor performance, organ dysfunction, poor follow-up or socioeconomic conditions, or active infection) may occur at the level of the treating investigator, leading to exclusion of patients and impact on outcome. Such biases cannot be accounted for, because the denominator from which patients were entered onto the study is not known. Nevertheless, despite the generally worse characteristics of the Hyper-CVAD study group, the regimen produced results comparable or superior to commonly used regimens (Table 4). This suggests that comparative trials of Hyper-CVAD and the "best standard of care" may be worthwhile.

In summary, treatment with Hyper-CVAD seems promising in adult ALL. Future modifications may involve incorporation of dose-intensive (perhaps liposomal encapsulated) anthracycline and asparaginase therapy during induction, selective novel agents (eg, Compound 506 for T-cell ALL)[70] or monoclonal antibodies (eg, rituximab for CD20-positive ALL; CAMPATH-1H), protein tyrosine kinase inhibitors targeted against the BCR-ABL protein in Ph-positive ALL,[71,72] improved supportive care in older patients, and allogeneic SCT in patients at high risk for sytemic relapse.

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