Long-Term Follow-Up Results of Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone (Hyper-CVAD), a Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia

Hagop Kantarjian, M.D.[1]
Deborah Thomas, M.D.[1]
Susan O'Brien, M.D.[1]
Jorge Cortes, M.D.[1]
Francis Giles, M.D.[1]
Sima Jeha, M.D.[1]
Carlos E. Bueso-Ramos, M.D.[2]
Sherry Pierce, R.N.[1]
Jianqin Shan, P.h.D.[1]
Charles Koller, M.D.[1]
Miloslav Beran, M.D., P.h.D.[1]
Michael Keating, M.B., B.S.[1]
Emil J. Freireich, M.D.[1]

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

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

BACKGROUND. Modern intensive chemotherapy regimens have improved the prognosis for patients with adult acute lymphocytic leukemia (ALL). With these regimens, the complete response rates are now reported to be $>$ 80%, and the long-term survival rates range from 30% to 45%. The current analysis updated the long-term results with the original hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) program, with a median follow-up time of 63 months.

METHODS. Between 1992 and 2000, 288 patients were treated with Hyper-CVAD. The median age of the patients was 40 years, and 59 patients (20%) were $\geq$ age 60 years. The incidence of Philadelphia chromosome (Ph)-positive ALL was 17%, and the incidence of of T-cell ALL was 13%.

RESULTS. A complete response (CR) was achieved in 92% of patients. The induction mortality rate was 5% (2% if the patient's age was $<$ 60 years, and 15% if the patient's age was $\geq$ 60 years). With a median follow-up time of 63 months, the 5-year survival rate was 38% and the 5-year CR duration rate was 38%. Multivariate analysis of prognostic factors for CR duration identified the following adverse factors: age $\geq$ 45 years, leukocytosis $\geq 50 \times 10^9$/L, poor performance status (an Eastern Cooperative Oncology Group score of 3–4), Ph-positive disease, French–American–British L2 morphology, $>$ 1 course to achieve CR, and Day 14 bone marrow blasts $>$ 5%. Patients were divided into low-risk (risk score 0–1; 37%), intermediate risk (risk score 2–3; 36%), and poor-risk groups (risk score $\geq$ 4; 27%) with 5-year CR duration rates of 52%, 37%, and 10%, respectively.

CONCLUSIONS. Compared with the previous VAD regimens, Hyper-CVAD was associated with significantly better CR rates, CR duration, and survival. The long-term follow-up results of Hyper-CVAD were favorable. Comparison of Hyper-CVAD with other established adult ALL regimens is warranted. ***Cancer* 2004;101: 2788–801.** © *2004 American Cancer Society.*

KEYWORDS: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) regimen, acute lymphocytic leukemia (ALL), long-term follow-up.

Modern intensive chemotherapy regimens have improved the prognosis for patients with adult acute lymphocytic leukemia (ALL). With these regimens, the complete response rates are now $>$ 80%, and the long-term survival rates range from 30% to 45%.[1–6] For the most part, the results have been confirmed in selected study groups, and the outcome is better for younger patients treated with these regimens.[7] The median age of the patients in older adult ALL

Address for reprints: Hagop Kantarjian, M.D., Department of Leukemia, P.O. Box 428, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030; Fax: (713) 794-4297; E-mail: hkantarj@mdanderson.org

Received May 12, 2004; revision received July 30, 2004; accepted August 16, 2004.

DOI 10.1002/cncr.20668
Published online 12 October 2004 in Wiley InterScience (www.interscience.wiley.com).

series was 25–30 years. In contrast, the median age of patients in more recent studies is 40–45 years,[2,5] reflecting the true adult age incidence in oncology community practice. Areas of significant concern to patient prognosis include older age (e.g., age 50 to ≥ 60 years), Philadelphia chromosome (Ph)-positive ALL, severe leukocytosis in patients with non–T-cell ALL (T-ALL), and slow response to induction therapy. Initial results concerning the Hyper-CVAD dose-intensive regimen, administered to adult patients with ALL were encouraging.[8] The current analysis updates our long-term results with the original Hyper-CVAD program, with a median follow-up time of 63 months.

MATERIALS AND METHODS

Study Group

Adults with previously untreated ALL were treated with Hyper-CVAD between February 1992 and March 2000. The protocol was approved by the institutional review board at The University of Texas M. D. Anderson Cancer Center (Houston, TX). Informed consent was obtained from patients according to institutional guidelines.

Entry criteria were age ≥ 15 years, and the absence of other active malignancy and expected consequent death within 12 months, as well as the absence of human immunodeficiency virus-1–positive status. No exclusions were made because of performance status or because of cardiac, hepatic, or renal function or concomitant active infection.

The diagnosis of ALL required the presence of lymphoid-looking blasts that were < 3% positive for myeloperoxidase and strongly positive (≥ 40%) for terminal deoxnucleotidyl transferase or demonstrated block positivity for periodic acid–Schiff (except for mature B-cell ALL [B-ALL]). Immunophenotyping and cytogenetic studies complemented the diagnosis in difficult cases.[8]

Pretreatment workup included history and physical examination; complete blood counts, differential, and platelet counts; serum chemistries (sequential multiple analysis 12/60), including liver and renal function studies; bone marrow aspiration for morphologic analysis and staining, and biopsy; cytogenetic analysis; and immunophenotyping. Classification of patient groups by karyotype and immunophenotype was reported in earlier studies.[8–10] Follow-up bone marrow studies were performed on Days 14 and 21 of disease remission induction, every 1–3 courses during consolidation, and every 3–6 months during maintenance. A positive immunophenotype referred to a cluster designation (CD) of ≥ 20%. Positive T-ALL referred to ≥ 2 T-cell markers (CD_1–CD_8). Common acute lymphoblastic leukemia antigen (CALLA) referred to expression of CD_{10} in addition to expression of CD_{19} or CD_{20}. Precursor B-ALL referred to expression of CD_{19} or CD_{20}. Mature B-ALL referred to expression of surface immunoglobulin (SIg) or clonal kappa or lambda. Patients were also tested for myeloid markers CD_{13}, CD_{14}, and CD_{33}. A positive myeloid marker required expression of one or more CDs. Five patients known to have Ph-positive ALL also had a ≥ 20% positive SIg. They also were positive for CD_{10} and CD_{19} or CD_{20}. We therefore considered them to be separate from the mature B-ALL category and in the CALLA ALL category.

Therapy

The regimen was comprised of two phases.

Dose-intensive phase

The dose-intensive phase included 8 cycles of dose-intensive therapy courses of Hyper-CVAD (Courses 1, 3, 5, and 7) alternating with high-dose methotrexate (MTX) and cytosine arabinoside (HD-MTX–Ara-C; Courses 2, 4, 6, and 8).

Hyper-CVAD. Hyper-CVAD was comprised of 300 mg/m^2 of cyclophosphamide administered intravenously (i.v.) over 2–3 hours every 12 hours for 6 doses on Days 1–3, with sodium mercaptoethanesulfonate given at twice the total dose as cyclophosphamide but given by continuous infusion starting with cyclophosphamide and ending 12 hours after the last dose; 2 mg of vincristine administered i.v. on Days 4 and 11; 50 $mg/m^2$of doxorubicin administered i.v. over 2 hours on Day 4; and 40 mg of dexamethasone daily on Days 1–4 and on Days 11–14.

HD-MTX-Ara-C. HD-MTX–Ara-C was comprised of 1 g/m^2 of MTX administered i.v. over 24 hours on Day 1; 15 mg of citrovorum factor rescue was initiated 12 hours after the completion of MTX infusion every 6 hours × 8, and increased to 50 mg i.v. every 6 hours if MTX levels were > 20 μmol/L at 0 hours, or were > 1.0 μmol/L at 24 hours, or were > 0.1 μmol/L at 48 hours after the end of MTX infusion, until levels were < 0.1 μmol/L; 3 g/m^2 of Ara-C was administered i.v. over 2 hours every 12 hours × 4 on Days 2 and 3; and 50 mg of methylprednisolone was administered i.v. twice daily on Days 1–3.

Central Nervous System Prophylaxis

Patients with a high risk for central nervous system (CNS) disease (lactate dehydrogenase level > 600 U/L [normal range, 25–225 U/L], or with a proliferative index [percent $S+G_2M$] ≥ 14% received 16 intrathecal treatments (IT). Patients with low risk (neither ele-

vated) received four IT. Patients with unknown risk (measurements were not available) received eight IT. Patients with mature B-ALL were included in the CNS high-risk category. CNS prophylaxis was given with 12 mg of MTX IT (6 mg if via the ommaya reservoir) on Day 2 and 100 mg of Ara-C IT on Day 8 of each cycle for 16 IT, 4 IT, or 8 IT as described. Patients at low or unknown risk for CNS disease received 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 cerebrospinal fluid study findings were negative and treatment then was received according to the schedule of the protocol. Patients with cranial nerve root involvement received 24–30 gray (Gy) of radiotherapy in 10–12 fractions, directed to the base of the skull or to the whole brain, during the disease remission induction.

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

Supportive care with granulocyte—colony-stimulating factor (G-CSF), 10 μg/kg daily, was given in 2 divided doses starting 24 hours after the end of chemotherapy (i.e., on Day 5 of Hyper-CVAD therapy and on Day 4 of HD-MTX–Ara-C therapy). Subsequent courses of chemotherapy were given as soon as the leukocyte count was $> 3 \times 10^9$/L and the platelet count was $> 60 \times 10^9$/L.

Dose Modifications

Vincristine was reduced to 1 mg if the bilirubin level was $>$ 2 mg/dL. The doxorubicin dose was reduced by 25% if the bilirubin level was 2–3 mg/dL, by 50% if it was 3–4 mg/dL, and by 75% if it was $>$ 4 mg/dL. The MTX dose was reduced by 25% when creatinine levels were 1.5–2 mg/dL and by 50% when levels were higher. The Ara-C dose was reduced to 1 g/m^2 in patients age $\geq$ 60 years, if the creatinine level was $>$ 2.0 mg/dL or if the MTX level at the end of the MTX infusion (0 hours after the completion of MTX therapy) was $\geq$ 20 μmol/L after repeat assays were performed.

Hyper-CVAD treatment courses (i.e., Courses 3, 5, and 7) did not usually require dose reductions for serious toxicities. With the HD-MTX–Ara-C treatment courses, serious toxicities (usually Grade 3–4 myelosuppression-associated complications other than neutropenia or thrombocytopenia) required subsequent dose reductions of 25–33% (i.e., the MTX dose was reduced to 750 mg/m^2 and then to 500 mg/m^2 and 250 mg/m^2 and the Ara-C dose was reduced to 2 g/m^2 and then to 1.5 g/m^2 and 1 g/m^2. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Mediastinal irradiation

Patients with T-ALL and mediastinal disease at the time of diagnosis underwent mediastinal irradiation at the end of intensive courses of chemotherapy and before maintenance. Patients received 30 Gy (range, 26–39.6 Gy; fraction size 1.5– 3 Gy) over a period of 3–4 weeks. Mediastinal irradiation was recommended regardless of the status of mediastinal disease after achievement of bone marrow complete remission (CR).

Maintenance phase

Patients with mature B-ALL received no maintenance therapy. Patients with Ph-positive ALL who were candidates for allogeneic stem cell transplantation (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 while in CR (without continuing the intensive phase).

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 at a dose of 50 mg orally 3 times daily (on an empty stomach), MTX at a dose of 20 mg/m^2 orally weekly, vincristine at a dose of 2 mg i.v. monthly, and prednisone at a dose of 200 mg orally daily $\times$ 5 every month (with vincristine). Since 1995, i.v. POMP was administered: 6-MP 1 g/m^2 given i.v. over 1 hour daily $\times$ 5 every month, MTX at a dose of 10 mg/m^2 i.v. given over 1 hour daily $\times$ 5 every month (with 6-MP), and vincristine and prednisone given 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) when moderate toxicity developed and by 50% (to 500 mg/m^2 and 5 mg/m^2, respectively) when severe toxicity occurred. Mucositis and hepatic dysfunctions were found to be related more to MTX therapy, and the MTX dose generally was reduced selectively before 6-MP dose reductions were considered.

Antibiotic prophylaxis given during the maintenance phase was comprised of trimethoprim-sulfamethoxazole given twice daily on weekends, and acyclovir at a dose of 200 mg or valacyclovir at a dose of 500 mg daily or 3 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

Survival was calculated from the initiation of therapy, and the CR duration was calculated from achievement of CR until there was evidence of leukemia recurrence (e.g., ≥ 10% of lymphoblasts in the bone marrow, or CNS or extramedullary disease recurrence). Survival and CR duration distributions were estimated using the Kaplan–Meier method, and were compared using the log-rank test. Differences in response rates were analyzed using a chi-square test. Significant cutoff points for prognostic factors were according to previously accepted categories, as well as visualization of the Martingale residual plots. A proportional hazards model was used to evaluate independent prognostic factors for survival and CR duration. Logistic regression analysis was used to identify independent prognostic factors for CR. In the design of the simplified multivariate-derived risk models, the 5-year survival or CR duration rates for each independent prognostic factor were assigned the following corresponding scores: > 35%, 0; 25–35%, 1; and < 25%, 2. Risk groups were then divided according to the aggregation/closeness of outcome in difference cumulative score categories.

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.[11] Entry criteria were similar during the two study periods.

RESULTS

Study Group

The characteristics of the 288 patients treated with Hyper-CVAD are summarized in Table 1. The median age of the patients was 40 years (mean, 42 years; range, 15–92 years), and 104 patients (36%) were age ≥ 50 years and 59 patients (20%) were age ≥ 60 years. The leukocyte count was ≥ 30×10^9/L in 73 patients (25%).

Therapy Results

Two hundred sixty-four patients (92%) achieved a CR, 14 (5%) died during induction, and 10 (3%) had resistant disease. Two hundred thirteen patients (81%) achieved a CR after 1 course of therapy. Induction death was caused by infections in 14 patients (i.e., fungal infection in 2 patients, bacterial infection in 3 patients, and multiple infections in 9 patients). The median time to CR was 22 days.

The median follow-up time was 63 months (range, 5–137 months). The median survival period was 32 months, the 5-year survival rate was 38%, and the 5-year CR rate was 38% (Figs. 1 and 2). At the time of last follow-up, 93 patients were alive without disease and 178 patients had died (i.e., induction deaths [$n = 14$], deaths due to disease recurrence [$n = 145$], and deaths while patients were in CR [$n = 19$]). The 19 deaths among patients in CR were caused by postallogeneic SCT complications in 3 patients with Ph-positive ALL, by infection-associated problems in 11 patients (sepsis in 9 patients and other causes in 2 patients), by organ failures in 3 patients (hepatic failure in 1 patient and neurotoxicity in 2 patients), and by old age in 2 patients. At the time of last follow-up, 11 patients (all with Ph-positive ALL) have undergone allogeneic SCT in first CR from related ($n = 7$) or unrelated donors ($n = 4$). Two (18%) of these patients were alive without disease for ≥ 64 and ≥ 74 months from SCT, respectively.

Response by pretreatment characteristics is shown in Table 2. The CR rate for patients age < 30 years was 99%, which is similar to the CR rate for childhood ALL. Patients age ≥ 60 years were found to have a lower CR rate (80%), mostly because of a higher induction mortality. Leukocytosis and karyotypic abnormalities were not associated with differences in CR rates. Patients with Ph-positive disease had a CR rate of 92%. Twenty patients had leukocytosis of ≥ 100×10^9/L, including 15 patients with non–T-ALL—19 (95%) of these patients achieved CR. Twelve patients had null-cell immunophenotypes. Of these, only 8 patients (67%) achieved a CR. Eight patients had a T-CALLA—precursor B phenotype (i.e., two or more positive T-cell markers [CD_{1-8}] in addition to a positive CD_{10} and CD_{19} or CD_{20}). Of these 8 patients, 6 (75%) achieved a CR.

There were no differences noted in CR rates by gender; presence of splenomegaly, adenopathy, mediastinal disease, or CNS disease; degree of anemia; presence of peripheral blasts; or presence of elevated levels of creatinine, lactate dehydrogenase, alkaline phosphatase, or β-2-microglobulin (data not shown). Patients with a poor performance status (Eastern Cooperative Oncology Group [ECOG] scale), hypoalbuminemia, hepatomegaly, or hyperbilirubinemia were found to have lower CR rates (68–82%), mostly because of high induction mortality rates: poor performance status, 40%; hypoalbuminemia, 24%; hepatomegaly, 16%; and hyperbilirubinemia, 19%. Among the 14 patients who experienced induction death, 9 (64%) were age ≥ 60 years, 6 (43%) had a poor performance status (ECOG score of 3–4), 9 (64%) had albumin levels < 3 mg/dL, 6 (43%) had elevated bilirubin levels, and 6 (43%) had hepatomegaly.

TABLE 1
Characteristics of the Study Group (n = 288)

Characteristics	No. of patients (%)	Characteristics	No. of patients (%)
Age (yrs)		t(8;14), t(2;8), t(8;22)	15 (5)
< 40	147 (51)	6q−; 14q +	19 (7)
40–59	82 (28)	Insufficient metaphases	59 (21)
≥ 60	59 (20)	Hyperdiploid	14 (5)
Performance score (ECOG scale)		Hypodiploid	13 (5)
3–4	19 (7)	Other	48 (17)
Splenomegaly		Not done	6 (2)
Yes	76 (26)	FAB classification	
Hepatomegaly		L1	93 (32)
Yes	44 (15)	L2	156 (54)
Lymphadenopathy		L3	31 (11)
Yes	91 (32)	Not classified/missing	8 (3)
CNS disease at diagnosis		Immunophenotype	
Yes	19 (7)	Mature B	27 (9)
Mediastinal mass		T	38 (13)
Yes	20 (7)	Precursor B	21 (7)
Leukocyte count ($\times 10^9$/L)		T-CALLA—precursor B	8 (3)
< 5	105 (36)	CALLA	159 (55)
5–49	135 (47)	Null	12 (4)
≥ 50	48 (17)	Not done	23 (8)
Platelet count ($\times 10^9$/L)		Myeloid markers	
≤ 80	193 (67)	Positive	128 (44)
Hemoglobin level (g/dL)		Negative	112 (39)
< 10	206 (72)	Not performed/unknown	48 (17)
Lactic dehydrogenase level (IU/L)		Systemic risk at CR (MDACC)	
> 600	147 (51)	Low	73 (25)
Alkaline phosphatase level (U/L)		High	212 (74)
≥ 80	202 (70)	Hoelzer risk at CR	
Creatinine level (mg/100 mL)		Low	67 (23)
≥ 1.3	40 (14)	High	221 (77)
Bilirubin level (mg/100 mL)		Risk for CNS disease	
≥ 1.3	35 (12)	High	158 (55)
Karyotype		Low	62 (22)
Diploid	66 (23)	Unknown	68 (24)
Ph positive	48 (17)		

ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system; CR: complete response; FAB: French–American–British; CALLA: common acute lymphoblastic leukemia antigen; MDACC: M. D. Anderson Cancer Center.

Multivariate analysis identified older age (age ≥ 60 years), thrombocytopenia (< 100×10^9/L), and T-CALLA—precursor B phenotype to be independently associated with worse CR rates ($P < 0.05$).

Survival and Disease Remission Duration

The overall survival of patients who received Hyper-CVAD is shown in Figure 1. Pretreatment characteristics associated with significant differences in survival rates are shown in Table 2. A multivariate analysis identified the following factors to be independent poor prognostic factors for survival ($P < 0.01$): older age, Ph-positive disease, leukocytosis, thrombocytopenia, poor performance (ECOG score of 3–4), and hepatomegaly. Patients were divided into good-risk (risk score 0–1; 37%), intermediate risk (risk score 2–3; 38%), or poor-risk groups (risk score ≥ 4; 26%) with estimated 5-year survival rates of 62%, 34%, and 5%, respectively (Tables 3 and 4; Fig. 3).

Disease remission duration with Hyper-CVAD is shown in Figure 2. Among patients achieving a CR, pretreatment factors associated with a worse disease remission duration are shown in Table 5. The need for > 1 course to achieve a CR, and the presence of bone marrow blasts > 5% on Day 14 also were found to be adverse factors. Multivariate analysis identified the following factors to be adverse independent factors for CR duration ($P < 0.05$): age ≥ 45 years; leukocytosis ≥ 50×10^9/L; poor performance (ECOG score of 3–4); Ph-positive disease; FAB L2 morphology; > 1 course to

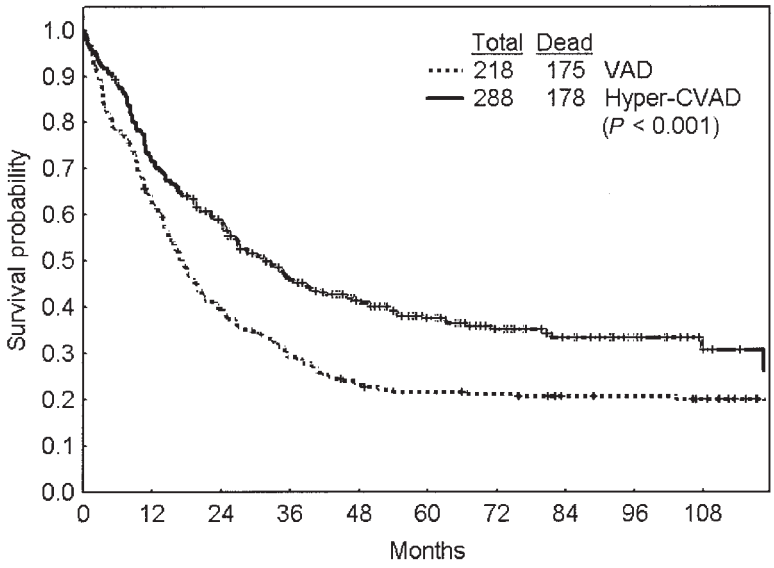

FIGURE 1. Survival with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) versus vincristine, doxorubicin, and dexamethasone (VAD).

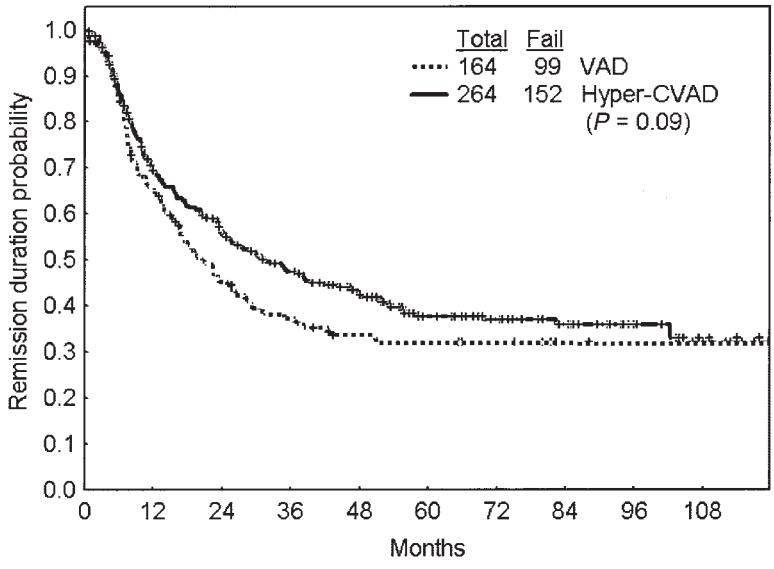

FIGURE 2. Disease remission duration with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) versus vincristine, doxorubicin, and dexamethasone (VAD).

CR; and bone marrow blasts > 5% on Day 14. Patients were divided into good-risk (risk score 0–1; 37%), intermediate risk (risk score 2–3; 36%), or poor-risk groups (risk score ≥ 4; 27%) with estimated 5-year CR duration rates of 52%, 37%, and 10% respectively (Tables 6 and 7; Fig. 4).

Comparison of Hyper-CVAD and VAD

The characteristics of patients who received Hyper-CVAD and VAD were similar except for a higher incidence of CNS disease at the time of presentation ($P = 0.048$), and a lower hemoglobin level ($P = 0.08$) with Hyper-CVAD.

The CR rates were found to be significantly better with Hyper-CVAD (Table 8), as were the survival and disease remission duration rates (Figs. 1 and 2).

There were no differences in survival or duration of disease remission duration noted with Hyper-CVAD based on whether patients received oral ($n = 103$) or i.v. POMP maintenance ($n = 83$). The 5-year survival rates were 53% and 55%, respectively ($P = 0.56$).

CNS Disease

Nineteen patients presented with CNS disease; 17 achieved both systemic and CNS disease remission and 11 patients developed disease recurrence (8 patients developed systemic disease and 3 patients developed CNS disease).

TABLE 2
Response and Survival by Pretreatment Characteristics

Characteristics	No. of CRs / Total	CR (%)	*P* value	5-Yr survival rate (%)	*P* value
Age (yrs)					
< 40	140/147	95		51	
40–59	77/82	94	< 0.001	30	< 0.001
≥ 60	47/59	80		17	
Performance score (ECOG)					
0–1	191/201	95		40	
2	60/68	88	< 0.001	37	< 0.001
3–4	13/19	68		12	
Hepatomegaly					
No	228/244	93	0.01	40	0.014
Yes	36/44	82		26	
Leukocyte count ($\times 10^9$/L)					
≤ 5	100/108	93		40	
5.1–49.9	121/132	92	0.821	44	< 0.001
≥ 50	43/48	90		16	
Platelet count ($\times 10^9$/L)					
< 20	24/29	83		24	
20–80	149/164	91	0.072	33	< 0.001
> 80	91/95	96		51	
Albumin level (mg/100 mL)					
< 3	42/52	81	0.002	40	0.39
≥ 3	222/236	94		38	
Bilirubin level (mg/100 mL)					
< 1.3	235/252	93	0.008	39	0.21
≥ 1.3	28/35	80		29	
FAB classification					
L1	87/93	94		48	
L2	143/156	92	0.525	29	0.038
L3	27/31	87		53	
Immunophenotype					
Mature B-cell ALL	24/27	89		36	
T-cell ALL	36/38	95		48	
T-CALLA—precursor B-cell ALL	6/8	75	0.005	16	0.18
Precursor B-cell ALL	21/21	100		45	
CALLA	149/159	94		38	
Null	8/12	67		25	
Karyotype					
Ph positive	44/48	92		12	
t(8;14), t(2;8), t(8;22)	14/15	93	0.96	67	< 0.001
Other	200/219	91		41	
Myeloid markers					
Positive	115/128	90		34	
Negative	104/112	93	0.595	41	0.66
Unknown	45/48	94		42	

CR: complete response; ECOG: Eastern Cooperative Oncology Group; FAB: French–American–British; CALLA: common acute lymphoblastic leukemia antigen.

Among 269 patients without initial CNS leukemia, 10 (4%) developed later CNS disease: none before systemic disease recurrence, 6 concomitant with bone marrow recurrence, and 4 after bone marrow recurrence. These included 4 (7%) of 60 patients with low-risk CNS disease, 2 (1%) of 145 patients with high-risk CNS disease, and 4 (6%) of 64 patients with unknown risk CNS.

Outcome in Subjects of Interest with ALL

Of 38 patients with T-ALL, 95% achieved a CR. Their 5-year continuous CR rate was 55%, compared with 35% for the other patients ($P = 0.04$). The 5-year survival rates were 48% and 36%, respectively ($P = 0.05$).

Twelve patients (4%) had T-ALL and mediastinal disease. One patient without mediastinal disease died

TABLE 3
Multivariate Analysis of Prognostic Factors for Survival rate (%)

Prognostic factor	No. of patients	Score assignment	5-Yr survival rate (%)	Multivariate analysis *P* value
Age (yrs)				
< 40	147	0	51	
40–59	82	1	30	< 0.0001
≥ 60	59	2	17	
Performance score (ECOG)				
0–2	269	0	39	< 0.0001
3–4	19	2	12	
Hepatomegaly				
No	244	0	40	0.006
Yes	44	1	26	
Leukocyte count ($\times 10^9$/L)				
< 50	240	0	42	0.0006
≥ 50	48	2	16	
Platelet count ($\times 10^9$/L)				
< 20	29	2	24	
20–80	164	1	33	0.0004
> 80	95	0	51	
Karyotype				
Other	234	0	42	0.0004
Ph	48	2	12	

ECOG: Eastern Cooperative Oncology Group; Ph: Philadelphia chromosome.

TABLE 4
Survival According to Risk Model

			Survival	
Prognostic model risk	Score	No. of patients (%)	Median (mos)	5-Yr survival rate (%)
Low	0–1	104 (37)	109	62
Intermediate	2–3	106 (38)	32	34
High	≥ 4	72 (26)	11	5

in CR after receipt of Course 8 of HD-MTX–Ara-C therapy. Two patients developed disease recurrence before the time of mediastinal irradiation. Mediastinal irradiation was performed for a total of 39.6 Gy, delivered in 22 fractions over 4.5 weeks (5 days on and 2 days off). Of the nine patients eligible for irradiation, seven received mediastinal irradiation and two of these seven patients developed disease recurrence (one in the bone marrow only and one in the mediastinum and bone marrow). Two of the nine patients who did not receive mediastinal irradiation developed disease recurrence (one in the bone marrow only and one in the bone marrow plus mediastinum and lymph nodes).

Among patients with Ph-positive ALL, 44 (92%) achieved a CR. Their 5-year survival rate was 12%. Eleven patients (25%) were eligible for and underwent allogeneic SCT; 6 developed disease recurrence after SCT, 3 died in CR after SCT, and 2 were alive in CR ≥ 68 months and ≥ 81 months, respectively, after SCT. Among the remaining 33 patients who achieved CR, 2 died in CR during consolidation, 12 developed disease recurrence during consolidation, 12 developed disease recurrence during maintenance therapy (6 after receiving interferon-α therapy), and 3 developed disease recurrence after maintenance therapy was completed. Thus, only 4 patients remained in CR after a median of 37 months (range, 21+ to 74+ months). These included two of five patients who also had SIg-positive, Ph-positive ALL.

Two patients (1%) had t(4;11)(q21;q23) translocations. Both patients achieved a CR but developed disease recurrence at 10 months and 16 months, respectively. Five patients had t(1;19). All 5 patients achieved a CR—1 patient died in CR at 3 months while receiving consolidation therapy, 1 patient developed disease recurrence at 9 months, and 3 patients were still alive in CR at the time of last follow-up at 57+ months, 73+ months, and 77+ months, respectively.

Side Effects

With induction chemotherapy (first course of Hyper-CVAD therapy), myelosuppression-associated complications were common. The median time to recovery of a granulocyte count $> 10^9$/L was 19 days, and was 22 days to a platelet count $> 100 \times 10^9$/L. Hospitalization for side effects was required for 54% of patients. Side effects included documented infections (sepsis in 11% of patients, pneumonia in 16% of patients, fungal infection in 4% of patients, and other minor infections in 8% of patients) and fever of unknown origin in 37% of patients. Other significant side effects included neurotoxicity, which was mostly steroid related (4%), moderate to severe mucositis (4%), moderate to severe diarrhea (3%), ileus (1%), and disseminated intravascular coagulopathy requiring therapy (3%).

The side effects during the Hyper-CVAD consolidation courses were modest. The median dose intensity delivery was 100%. Myelosuppression-associated side effects included documented infections (10%: sepsis, 4%; pneumonia, 2%; herpes, 0.5%; cytomegalovirus [CMV] infection, 1%; minor infections, 4%) and fever of unknown origin (8%). Hospitalization for side effects was required after receipt of 16% of courses. Other significant side effects included neurotoxicity (7%), mostly steroid-associated mood changes or depression, mucositis and diarrhea (1%), cardiac complications (1%), and G-CSF therapy-associated bone aches (7%). The median time to recovery of counts and delivery of the next course was 20 days.

Myelosuppression-associated complications were

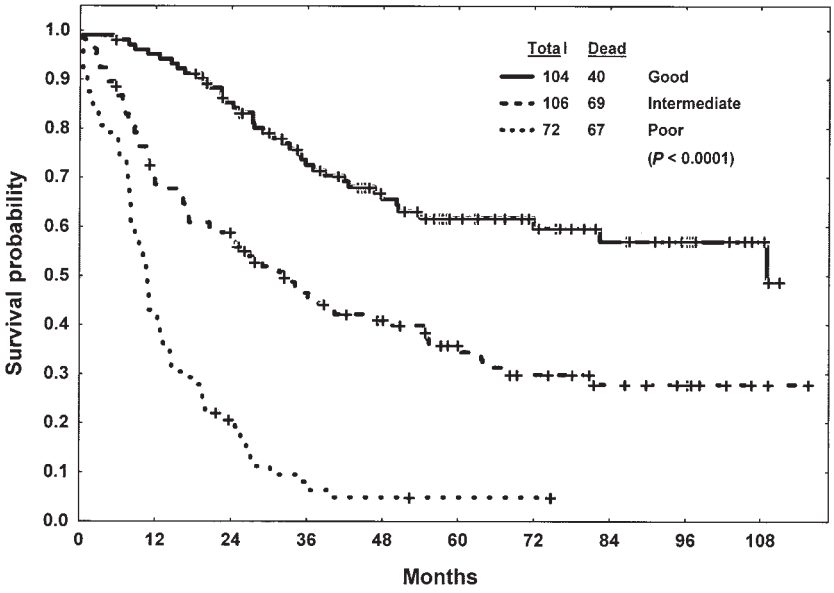

FIGURE 3. Survival with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with the presence of none or one, two to three, or four or more 4 adverse factors.

more frequent with HD-MTX–Ara-C therapy. These included sepsis (8%), pneumonia (5%), fungal infections (0.5%), herpes (2%), CMV infection (1%), minor infections (4%), and fever of unknown origin (22%). Other side effects were renal and hepatic toxicities (1.5%), neurotoxicity (5%), skin rashes (4%), rash and desquamation of the palms and feet (2%), mucositis (4%), diarrhea (1%), Ara-C therapy-associated fever (4%), and G-CSF therapy-associated bone aches (1%). Reversible renal failure (creatinine levels $\geq$ 3 mg/100 mL) from MTX therapy occurred in 9 patients. Hospitalization for side effects was needed after receipt of 36% of the courses.

The median dose intensity delivered was 100%. MTX dose reductions were required—to 75% in 16% of courses, to 50% in 12% of courses, and to 25% in 2% of courses. Dose reductions of ara-C were required in 32% of courses, mostly for patients age $>$ 60 years (1 g/m^2; 16% of courses). The median time to recovery and delivery of the next course was 22 days. The median time to delivery of all 8 courses was 5.8 months (range, 4–9 months).

With the POMP maintenance, the median dose of 6-MP delivered was 150 mg daily, the median MTX dose was 15 mg/m^2 weekly, and the median vincristine/prednisone delivery was 100% monthly. Three patients developed late acute myeloid leukemia (n = 1) or myelodysplastic syndrome (n = 2) after 34 months, 40 months, and 47 months, respectively.

Unusual side effects included herpes zoster or varicella (n = 17 [6%]), CMV infection (n = 10 [4%]), and *Pneumocystis* infection (n = 3 [1%]). Fungal infections occurred in 10 patients (4%) during induction, and in 3 patients (1%) during consolidation maintenance. Death during disease remission occurred in 19 patients (the causes were detailed earlier in the text).

DISCUSSION

The long-term follow up results with Hyper-CVAD are encouraging. Two hundred sixty-four of 288 patients (92%) who were treated achieved CR. The induction mortality rate was very low overall (5%), but was higher in patients age $>$ 60 years compared with younger patients (15% vs. 2%; $P < 0.001$). With a median follow-up time of 63 months, the 5-year survival rate was 38% and the 5-year CR duration rate was 38%. Side effects were as expected, mostly attributed to myelosuppression. No unexpected long-term toxicities occurred.

Prognostic factors for long-term outcome were similar to those reported in previous studies.[1–7] Older patients had a worse outcome because of both increased induction–consolidation-associated mortality and disease recurrence. Ph-positive ALL, leukocytosis, and residual disease after disease remission induction were adverse prognostic factors for long-term outcome. Based on our update, we propose simplified prognostic models for both survival and disease remission duration (Tables 3, 4, and 6). The latter divided patients into low-risk (37%), intermediate risk (36%), and high-risk (27%) groups with corresponding 5-year disease remission rates of 52%, 37%, and 10%, respectively (Fig. 4).

Ph-positive ALL remains a poor-risk disease with chemotherapy alone.[9–12] In patients eligible to undergo allogeneic SCT, such a procedure should be

TABLE 5
Complete Disease Remission Duration by Patient Characteristics

Characteristics	No. of patients	5-Yr CR rate (%)	*P* value
All patients	264	38	—
Age (yrs)			
< 30	91	40	0.008
30–44	65	48	
45–59	61	31	
≥ 60	47	27	
Performance score (ECOG)			
0–2	251	39	0.005
3–4	13	9	
Leukocyte count ($\times 10^9$/L)			
≥ 5	100	35	< 0.001
5.1–30	97	47	
> 30–49	24	38	
≥ 50	43	19	
Platelet count ($\times 10^9$/L)			
< 20	24	32	0.223
20–80	149	34	
81–99	21	50	
≥ 100	70	44	
Immunophenotype			
Mature B	24	43	0.221
T-CALLA Pre-B	6	25	
T	36	55	
Precursor-B	21	58	
CALLA	149	32	
Null	8	33	
Karyotype			
Ph positive	44	14	< 0.001
t (8;14), t (2;8), t (8;22)	14	76	
Other	200	39	
FAB			
L1	87	44	0.002
L2	143	28	
L3	27	67	
No. of courses to CR			
1	213	42	< 0.001
> 1	51	18	
Systemic risk group (MDACC)			
Low	69	44	0.016
High	193	36	
Hoelzer risk group			
Low	67	45	0.020
High	197	35	
Day 14 bone marrow blasts > 5%			
Yes	81	25	0.003
No	155	42	

CR: complete responses; ECOG: Eastern Cooperative Oncology Group; CALLA: common acute lymphoblastic leukemia antigen; Ph: Philadelphia chromosome; FAB: French–American–British; MDACC: M. D. Anderson Cancer Center.

TABLE 6
Multivariate Analysis of Prognostic Factors Associated with Disease Remission Duration

Prognostic factor	No. of patients	Score assignment	5-Yr CR duration	Multivariate analysis *P* value
Age (yrs)				
< 45	156	0	43	0.0006
≥ 45	108	1	29	
Performance score (ECOG)				
0–2	251	0	39	0.002
3–4	13	2	9	
Leukocyte count ($\times 10^9$/L)				
< 50	221	0	41	< 0.0001
≥ 50	43	2	19	
FAB morphology				
Other	114	0	49	0.02
L2	143	1	28	
Karyotype				
Other	214	0	41	0.002
Ph	44	2	14	
No. of courses to CR				
1	213	0	42	0.04
≥ 2	51	2	18	
Day 14 bone marrow blasts (%)				
≤ 5	155	0	42	0.01
> 5	81	1	25	

CR: complete response; ECOG: Eastern Cooperative Oncology Group; FAB: French–American–British.

TABLE 7
Duration of Remission According to Risk Model

Prognostic model risk	Score	No. of patients (%)	CR duration	
			Median (mos)	5-yr survival rate (%)
Low	0–1	83 (37)	120	52
Intermediate	2–3	82 (36)	40	37
High	≥ 4	62 (27)	9	10

CR: complete response.

performed as soon as possible while patients are in first CR.[13–15] However, even under optimal conditions, the results are modest. In the study by Goldstone et al.,[14] 267 of 1389 patients (19%) in the UKALL12/ECOG Intergroup study had Ph-positive ALL. In that study, the CR rate was 76%, the 5-year survival rate was 23%, and the event-free survival (EFS) rate was 18%. The 5-year EFS rate was 37% for patients with Ph-positive ALL who had related donors and 27% for those who did not have related donors.[14] Barrett et al.[15] reported that the 5-year EFS rate was 22–35% for patients with Ph-positive ALL who had undergone allogeneic SCT in first CR or after disease recurrence. Recent data with Hyper-CVAD plus imatinib mesylate are encouraging.[10] Among 16 patients treated with this regimen for newly diagnosed Ph-positive ALL, the CR rate was 100% and the estimated 2-year survival rate was 85%.

The role of allogeneic SCT in first CR is evolving.

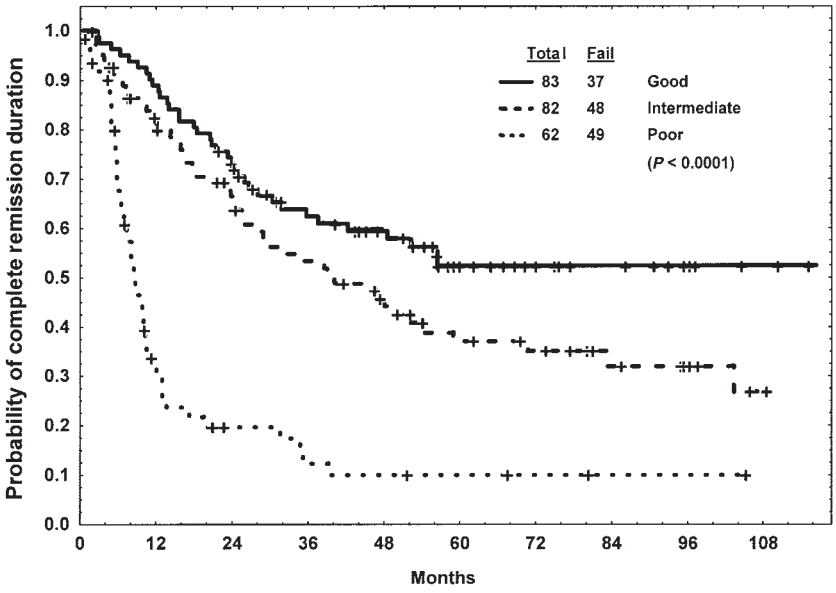

FIGURE 4. Duration of disease remission with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with the presence of none or one, two to three, or four or more adverse prognostic factors.

TABLE 8
Response with Hyper-CVAD Versus VAD

Response	Hyper-CVAD (n = 288) (%)	VAD (n = 218) (%)	P value
Complete response			
Overall	92	75	< 0.001
After Course 1	81	73	0.05
Induction mortality	5	5	NS
Resistant disease	3	20	< 0.001
Bone marrow blasts > 5% on Day 14	34	48	0.005

Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; VAD: vincristine, doxorubicin, and dexamethasone.

Earlier studies had demonstrated no advantage of allogeneic SCT versus chemotherapy in the first CR overall,[17] but a potential advantage in patients with high-risk ALL (defined as Ph-positive ALL, a longer time to CR, or leukocytosis in non–T-ALL).[18] A recent Medical Research Council (MRC)-ECOG Intergroup trial in adult ALL suggested a benefit from allogeneic SCT in first CR in all risk categories for patients ages 15–50 years, but to our knowledge the final results have not been reported.[19] Our current institutional recommendation is to offer allogeneic SCT to patients with high-risk ALL in first CR with acceptable risk from SCT. In the future, this may change to include all patients ages 15–50 years in first CR depending on the final results of the MRC-ECOG trial.

The method of CNS prophylaxis is also changing in adult ALL. In the current study, CNS prophylaxis with IT risk-targeted therapy and high-dose chemotherapy was associated with an overall CNS disease recurrence rate of only 4%. Similar experiences were reported in childhood ALL.[20,21] Thus, future studies will likely replace craniospinal irradiation with IT plus high-dose systemic chemotherapy, which alleviates some of the irradiation-associated complications.[22,23]

The value of individual components of the total adult ALL programs is being clarified. Recent studies in childhood ALL have confirmed the superiority of dexamethasone to prednisone in relation to lower incidences of CNS and systemic disease recurrences.[24–26] Using more dose-intensive regimens and increasing the frequency of delivery of nonmyelosuppressive drugs (vincristine, steroids, and asparaginase) was found to improve the cure rates in childhood ALL, but these agents are difficult to deliver to adults with ALL, particularly asparaginase.[27–30] Two recent analyses compared pediatric with adult ALL regimens delivered to adolescents and young adults with ALL (age range, 15–20 years).[31,32] Both suggested a survival advantage for pediatric regimens. In a study comparing the outcome of the pediatric FRALLE-93 with the adult LALA-94 French studies in adolescents with ALL (ages, 15–20 years), the reported CR rates were 94% versus 83% ($P = 0.04$), and the estimated 5-year EFS rates were 67% versus 41% ($P < 0.0001$).[32] Similarly, a comparison of the pediatric Children's Cancer Group and adult Cancer and Leukemia Group B (CALGB) studies in adolescents with ALL (ages, 16–21 years) demonstrated CR rates of 96% versus 93% (P values were not significant), but the estimated 6-year EFS rates were 64% versus 38% ($P < 0.01$).[31] This is perhaps due to better regimen intensity tolerance and delivery, better compliance of younger patients/pediatric oncologists to regimen delivery, or, quite likely, less intensity

TABLE 9
Summary of Large Adult ALL Studies

Study (reference)	No. entered / evaluable	Median age (yrs)	Percent age > 60 yrs	CR (%)	Mortality (%)	Median survival/ CR duration (mos)	Survival/CR duration percent (at X yr)
Hoelzer et al.[37]	384/368	25	0	74	11	28/24	39 (5)/37 (5)
Durrant et al.[3]							
UK ALL 1X	266	—[a]	—[a]	87	—[a]	—[a]	—/26 (5)
UK ALL XA	618	—[a]	—[a]	88	—[a]	—[a]	—[a]/28 (5)
UK ALL—ECOG	1330	(age 15–55)	0	89	—[a]	—[a]	—[a]/38 (5)
Thiebaut et al.[4]	634/572	33	0	76	9	18/—[a]	27 (10)/—[a]
Larson[5]/Stock et al.[43]							
8011	197	32		85	—[a]	28/29	43 (5)/42 (5)
9111	198	35		82	7	26/24	—[a]
9311	82/78	35		85	—[a]	—[a]	45 (3)/41 (3)
A-B-C regimen	163	41		78	11	19/18	—[a]
Hyper-CVAD	288	40		92	5	32/32	38 (5)/38 (5)

ALL: acute lymphoblastic leukemia; CR: complete response; UK: United Kingdom; ECOG: Eastern Cooperative Oncology Group; A-B-C regimen: anthracycline, methotrexate, and cytosine arabinoside; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.
[a] Not available.

maintenance in adult ALL programs with the underappreciated but quite effective four-drug POMP combination. Analysis of the total doses of these four drugs delivered in pediatric versus adult regimens may help to clarify this issue.[33–35] Conversely, the MRC studies using identical regimens for pediatric and adult ALL (UKALL trials X and XA) found significant survival differences by age. The 10-year survival rates by age group were 0-9, 62%; 10–14, 49%; 15–19, 35%; 20–39, 29%; and $\geq$ 40, 15%.[36] In contrast to the previous opinions, they concluded that pediatric regimens were not adequate for the treatment of adult ALL.[3,36] With Hyper-CVAD, 92 patients (32%) were age $\leq$ 30 years. Their CR rate was 99% and their 5-year survival rate was 51%, which is similar to the pediatric ALL regimens, despite a significantly older median age of the patients (22 years vs. 15 years and 16 years, respectively).

Also of interest is the outcome of patients with ALL at the other age extreme, namely patients age $\geq$ 60 years. Many studies exclude these patients specifically,[7,37] some experts advocate only supportive care for these older patients,[38] and trials that include them report 3-year survival rates of $<$ 15% for patients age $>$ 55–60 years.[2–5] The 5-year survival rate for patients age $\geq$ 60 years who received Hyper-CVAD was 17% and the 5-year CR duration rate was 27%. This suggests a definite benefit for Hyper-CVAD in such patients, which may be superior to other regimens.

The duration of maintenance therapy was investigated recently in studies from Japan with more dose-intensive regimens.[39] Shorter maintenance durations (i.e., lasting 1 year) were associated with worse outcome than longer maintenance durations (i.e., lasting 2–3 years). Intravenous POMP was not found to be superior to oral POMP therapy in our programs, and may have yielded worse results in pediatric studies.[40,41]

Comparison of different adult ALL regimens is difficult because of different entry criteria (Table 9). There were no exclusions by age with Hyper-CVAD. Patients age $\geq$ 65 years were excluded from the early Berlin-Frankfurt Munster (BFM) studies,[37] and those age $\geq$ 60 years were excluded in the Linker et al. regimens.[7] The median age in our study group was 40 years, compared with median age ranges of 25–32 years in other adult ALL regimens.[37] The incidence of patients age $\geq$ 60 years was 22% with Hyper-CVAD versus 9% in the recent CALGB studies.[42] The more recent CALGB studies, in which the median age of the patients currently is approximately 40 years, yielded worse long-term results.[5,43] In a recent update of the latest CALGB study using the A-B-C regimen (anthracycline dose-intensive induction, high-dose MTX, and Ara-C consolidations), 163 adults with ALL were treated. Their median age was 41 years. The CR rate was 78% and the induction mortality rate was 11%. The median survival period was 1.6 years and the median disease-free survival period was 1.5 years. This may be due to inclusion of worse prognosis patients in the more recent CALGB studies.[43] In the current study, there were no exclusions for poor performance staus, organ dysfunction, or Ph-positive ALL (the latter category was excluded from some programs [e.g., the Linker et al. regimen[7]] whereas the BFM regimen included only a "few" such patients[37]). Nevertheless, Hyper-CVAD was associated with favorable results, such as a CR rate of 92%, an induction mortality rate

of 5%, a median survival period of 32 months, and a 5-year survival rate of 38%. Future studies that compare, in randomized trials, the Hyper-CVAD regimen with other established programs should be conducted.

The Hyper-CVAD experience has cross-fertilized other areas of research in hematologic cancers. First studied in patients with adult ALL, Hyper-CVAD later demonstrated benefit in several other hematologic malignancies including lymphoblastic lymphoma,[44] mantle cell lymphoma-leukemia,[45,46] multiple myeloma,[47] Richter transformation of chronic lymphocytic leukemia,[48] and other lymphomas. Longer-term follow-up for patients with these other malignancies receiving the Hyper-CVAD regimen will help to place the currently reported data in context.

Current and future investigations should focus on improving the results in patients with adult ALL. This may be accomplished with more dose-intensive programs, the use of allogeneic SCT during the first CR in all eligible patients, combining chemotherapy plus imatinib in the treatment of patients with Ph-positive ALL, incorporating monoclonal antibody therapy in patients whose leukemic cells express the appropriate target (e.g., rituximab if CD_{20} positive, alemtuzumab if CD_{52} positive, and gemtuzumab if CD_{33} positive), including new chemotherapy agents into ALL regimens (e.g., C506U in T-ALL), prolonging the duration of maintenance therapy, and discovering new agents with anti-ALL activity.

REFERENCES

1. Faderl S, Jeha S, Kantarjian H. The biology and therapy of adult acute lymphoblastic leukemia. *Cancer*. 2003;98:1337–1354.
2. Gokbuget N, Hoelzer D, Arnold R, et al. Treatment of adult ALL according to protocols of the German Multicenter study group for adult ALL (GMALL). *Hematol/Oncol Clin North Am*. 2000;14:1307–1325.
3. Durrant IJ, Richards SM, Prentice HG, Goldstone AH. The Medical Research Council trials in adult acute lymphocytic leukemia. *Hematol/Oncol Clin North Am*. 2000;14:1327–1352.
4. Thiebaut A, Vernant JP, Degos L, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation: a follow-up report of the French protocol LALA 87. *Hematol/Oncol Clin North Am*. 2000;14:1353–1365.
5. Larson RA. Recent clinical trials in acute lymphocytic leukemia by the Cancer and Leukemia Group B. *Hematol/Oncol Clin North Am*. 2000;14:1367–1379.
6. Garcia-Manero G, Kantarjian H. The Hyper-CVAD regimen in adult acute lymphocytic leukemia. *Hematol/Oncol Clin North Am*. 2000;14:1381–1396.
7. Linker CA, Levitt LJ, O'Donnell M, et al. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. *Blood*. 1991;78:2814–2822.
8. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000;18:547–561.
9. Faderl S, Garcia-Manero G, Thomas DA, Kantarjian HM. Philadelphia chromosome-positive acute lymphoblastic leukemia—current concepts and future perspectives. *Rev Clin Exp Hematol*. 2002;6:142–160.
10. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. 2004;103:4396–4407.
11. Kantarjian HM, Walters RS, Keating MJ, et al. Results of the vincristine, doxorubicin and dexamethasone regimen in adults with standard- and high-risk acute lymphocytic leukemia. *J Clin Oncol*. 1990;8:994–1004.
12. Wetzler M, Dodge RK, Mrozek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the Cancer and Leukemia Group B experience. *Blood*. 1999;93:3983–3993.
13. Goldstone AH, Prentice HG, Durant J, et al. Allogeneic transplant (related or unrelated donor) is the preferred treatment for adult Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). Results from the International ALL Trial (MRC UKALLXII/ECOG E2933) [abstract]. *Blood*. 2001;98:856a.
14. Goldstone A, Chopra R, Buck G, et al. The outcome of 267 Philadelphia positive adults in the International UKALL12/ECOG E 2993 study. Final analysis and the role of allogeneic transplant in those under 50 years [abstract]. *Blood*. 2003;102:80a
15. Barrett A, Horowitz M, Ash R, et al. Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 1992;79:3067–3070.
16. Hoelzer D. Which factors influence the different outcome of therapy in adults and children with ALL? *Bone Marrow Transplant*. 1989;4(Suppl. 1):98–100.
17. Zang M, Hoelzer D, Horowitz M, et al. Long-term follow-up of adults with acute lymphoblastic leukemia in first remission treated with chemotherapy or bone marrow transplantation. *Ann Intern Med*. 1995;123:428–431.
18. Sebban C, Lepage E, Vernant J, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. *J Clin Oncol*. 1994;12:2580–2587.
19. Rowe JM, Richards S, Burnett AK, et al. Favorable results of allogeneic bone marrow transplantation (BMT) for adults with Philadelphia (Ph)-chromosome-negative acute lymphoblastic leukemia (ALL) in first complete remission (CR): results from the International ALL Trial (MRC UKALL XII/ECOG E2993) [abstract]. *Blood*. 2001;98:481a.
20. Nachman J, Sather H, Cherlow J, et al. Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: A report from the Children's Cancer Group. *J Clin Oncol*. 1998;16:920–930.
21. Bürger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. *J Clin Oncol*. 2003;21:184–188.
22. Pui C-H, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. *N Engl J Med*. 2003;349:640–649.

23. Walter A, Hancock M, Pui C-H, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St. Jude children's Research Hospital. *J Clin Oncol.* 1998; 16:3761–3767.
24. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood.* 2003;101:3809–3817.
25. Norwak-Göttl U, Ahlke E, Fleischhack G, et al. Thromboembolic events in children with acute lymphoblastic leukemia (BFM protocols): prednisone versus dexamethasone administration. *Blood.* 2003;101:2529–2533.
26. Schwartz C, Thompson EB, Gelber R, et al. Improved response with higher corticosteroid dose in children with acute lymphoblastic leukemia. *J Clin Oncol.* 2001;19:1040–1046.
27. Pui C-H, Evans WE. Acute lymphoblastic leukemia. *N Engl J Med.* 1998;339:605–615.
28. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90—German-Austrian-Swiss ALL-BFM Study Group. *Blood.* 2000;95:3310–3322.
29. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana Farber Consortium Protocol 91-01. *Blood.* 2001;97:1211–1218.
30. Nachman JB, Harland NS, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N Engl J Med.* 1998;338:1663–1671.
31. Stock W, Sather HN, Dodge RK. Outcome of adolescents and young adults with ALL: a comparison of Children's Cancer Group (CCG) and Cancer and Leukemia Group B (CALGB) regimens [abstract]. *Blood.* 2000;96:467a.
32. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J Clin Oncol.* 2003;21:774–780.
33. Schiffer CA. Differences in outcome in adolescents with acute lymphoblastic leukemia: a consequence of better regimens? Better doctors? Both? *J Clin Oncol.* 2003;21:760–761.
34. Peeters M, Koren G, Jakubovicz D, et al. Physician compliance and relapse rates of acute lymphoblastic leukemia in children. *Clin Pharmacol Ther.* 1988;43:228–232.
35. Eden OB, Stiller CA, Gerrard MP. Improved survival for childhood acute lymphoblastic leukemia: possible effect of protocol compliance. *Pediatr Hematol Oncol.* 1988;5:83–91.
36. Chessells J, Hall E, Prentice H, et al. The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XA compared: a report from the MRC Paediatric and Adult Working Parties. *Leukemia.* 1998;12:463–473.
37. Hoelzer D, Thiel E, Löffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood.* 1988;71:123–131.
38. Taylor PRA, Reid MM, Brown N, Hamilton PJ, Proctor SJ. Acute lymphoblastic leukemia in patients aged 60 years and over: a population-based study of incidence and outcome. *Blood.* 1992;80:1813–1817.
39. Toyoda Y, Manabe A, Tsuchida M, et al. Six months of maintenance chemotherapy after intensified treatment for acute lymphoblastic leukemia of childhood. *J Clin Oncol.* 2000;18;1508–1516.
40. Lauer S, Shuster J, Mahoney D, et al. A comparison of early intensive methotrexate/metcaptopurine with early intensive alternating combination chemotherapy for high-risk B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group phase III randomized trial. *Leukemia.* 2000;15:1038–1045.
41. Schmiegelow K, Björk O, Glomstein A, et al. Intensification of mercaptopurine/methotrexate maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic leukemia. *J Clin Oncol.* 2003;21:1332–1339.
42. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and Leukemia Group B study 8811. *Blood.* 1995;85:2025–2037.
43. Stock W, Yu D, Johnson J, et al. Intensified daunorubicin during induction and post-remission therapy of adult acute lymphoblastic leukemia (ALL): results of CALGB 19802 [abstract]. *Blood.* 2003;102:379a.
44. Thomas D, O'Brien S, Cortes J, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. *Blood.* 2004;104:1624–1630.
45. Romaguera JE, Khouri IF, Kantarjian H, et al. Untreated aggressive mantle cell lymphoma: results with intensive chemotherapy without stem cell transplant in elderly patients. *Leuk Lymphoma.* 2000;39:1–9.
46. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high dose methotrexate/cytarabine followed by stem cell transplantation: an active regimen for aggressive mantle cell lymphoma. *J Clin Oncol.* 1998;16:3803–3809.
47. Dimopoulos MA, Weber D, Kantarjian H, et al. HyperCVAD for VAD-resistant multiple myeloma. *Am J Hematol.* 1996; 52:77–81.
48. Tsimberidou AM, Kantarjian H, Cortes J, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Cancer.* 2003;97: 1711–1720.