Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma

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Therapy of lymphoblastic lymphoma (LL) has evolved with use of chemotherapy regimens modeled after those for acute lymphocytic leukemia (ALL). We treated 33 patients with LL with the intensive chemotherapy regimens hyper–CVAD (fractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone) or modified hyper-CVAD used for ALL at our institution. Induction consolidation was administered with 8 or 9 alternating cycles of chemotherapy over 5 to 6 months with intrathecal chemotherapy prophylaxis, followed by maintenance therapy. Consolidative radiation therapy was given to patients with mediastinal disease at presentation. No consolidation with autologous or allogeneic stem cell transplantation was performed. At diagnosis, 80% were T-cell immunophenotype, 70% were stages III to IV, 70% had mediastinal involvement, and 9% had central nervous system (CNS) disease. Of the patients, 30 (91%) achieved complete remission, and 3 (9%) achieved partial response. Within a median of 13 months, 10 patients (30%) relapsed or progressed. Estimates for 3-year progression-free and overall survival for the 33 patients were 66% and 70%, respectively. Estimates for the patients with known T-cell immunophenotype were 62% and 67%, respectively. No parameters (eg, age, stage, serum lactate dehydrogenase [LDH], β_2 microglobulin) appeared to influence outcome except for CNS disease at presentation. Modification of the hyper-CVAD regimen with anthracycline intensification did not improve outcome. Other modifications of the program could include incorporation of monoclonal antibodies and/or nucleoside analogs, particularly for slow responders or those with residual mediastinal disease. (Blood. 2004;104:1624-1630)

Introduction

Lymphoblastic lymphoma (LL) represents 2% to 4% of adult non-Hodgkin lymphomas (NHLs).[1] This high-grade lymphoma has several distinct clinicopathologic features. Clinically, it often presents with mediastinal and supradiaphragmatic lymph node involvement, manifesting as cough, shortness of breath, respiratory distress, and/or superior vena cava (SVC) syndrome.[2-6] Central nervous system (CNS) involvement at presentation occurs in 20% of cases and is a frequent site of relapse in the absence of CNS prophylaxis.[2-6] Morphologically, the lymphoblasts are medium-to-large in size and have a typical convoluted nuclei appearance, staining brightly for terminal deoxynucletidyl transferase (TdT).[4-7] Higher mitotic rates are observed when compared with French-American-British (FAB) L1 or L2 lymphoblasts.

When evaluated by immunophenotyping, most LLs are of T-cell origin. Non–T-cell LL occurs in 5% to 20% of cases, often has a different clinical presentation (younger age, female preponderance, higher incidence of skin involvement), and has a better prognosis.[8] When LL involves the marrow or progresses to a leukemic phase (> 25% marrow blasts), it may be indistinguishable from T-cell acute lymphocytic leukemia (ALL). Although these disorders likely represent the same spectrum of disease with different presentations, features such as presence or absence of lymphadenopathy, splenomegaly, and/or thrombocytopenia may differentiate the 2 entities and further delineate prognosis.[1,9,10]

Prior to the application of intensive ALL regimens to LL, prognosis was poor. With lymphoma-like regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and asparaginase, complete response (CR) rates ranged from 40% to 70% with disease-free survival (DFS) rates of 20% to 50%.[1-3,7] With ALL-type chemotherapy regimens, CR rates were 70% to 80%, and DFS rates, 30% to 50%.[2,11-16] While it is difficult to ascertain the superiority of regimens designed for ALL over those used for lymphomas given the heterogeneity of the regimens, a few generalizations can be made. More intensive chemotherapy regimens appear to be superior to less intensive regimens, shorter-term chemotherapy regimens without maintenance therapy appear to increase the risk of relapse, and intensive CNS prophylaxis is required to reduce the incidence of CNS relapse.[1,17-19] This report summarizes the experience with hyper–CVAD[20] (fractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone) and modified hyper-CVAD[21] dose-intensive regimens used for adult ALL at our institution, in patients with LL.

Patients, materials, and methods

Study group

From April 1992 until November 2001, 33 patients with a new diagnosis of LL were treated with the standard or modified hyper-CVAD regimens, with

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informed consent obtained according to institutional review board guidelines at M.D. Anderson Cancer Center. All patients were required to have documentation of LL by tumor tissue sampling of involved sites, with classification performed by either the updated Kiel-Classification[22] for NHL or the Revised European American Lymphoma Classification.[23] Eligibility criteria included age 15 years or older, performance status 3 or better, adequate renal and hepatic functions (serum creatinine $\leq$ 265.2 μM [3 mg/dL] and bilirubin $\leq$ 51.3 μM [3 mg/dL] unless related to disease), absence of other active malignancy with expected consequent death within 12 months, or human immunodeficiency virus-1 (HIV-1)–positive status. There were no exclusions by concomitant active infections or by pretreatment cardiac function.

Assessments

Pretreatment evaluations included history and physical examination, complete blood count with differential, sequential multiple analysis-12 including lactate dehydrogenase (LDH), and bone marrow aspiration for histology, flow cytometry, and cytogenetic studies. Cytogenetic analysis was performed by standard techniques, with bone marrow specimens examined on direct or short-term (24-hour) cultures.[24] Karyotypic categories were according to previously reported nonrandom chromosomal abnormalities of defined significance in ALL.[25]

Clinical staging was performed according to the Ann Arbor classification.[26] Chest roentgenograms (CXRs) were performed on all patients. Other radiologic studies (eg, computerized tomography of chest and abdomen) were done as clinically indicated. Baseline cardiac function was assessed by echocardiogram or multigated radionuclide ventriculography (MUGA) scan in patients with cardiac risk factors. The presence or absence of CNS disease was evaluated in all patients concurrently with administration of CNS prophylaxis with methotrexate (approximately day 2 of the first course). Cerebrospinal fluid was assessed by cell count with differential and cytologic evaluation.

Therapy

Hyper-CVAD. Therapy consisted of the standard hyper-CVAD program as previously detailed (Figure 1).[20] Treatment was given with 8 induction-consolidation courses alternating hyper-CVAD with high-dose methotrexate and cytarabine. Briefly, the treatment regimen was as follows. Odd courses (1, 3, 5, 7) were hyper-CVAD: hyper-fractionated cyclophosphamide (CTX) given 300 mg/m^2 intravenously over 2 hours every 12 hours for 6 doses on days 1 to 3 with 600 mg/m^2 Mesna daily intravenously via continuous infusion on days 1 to 3 beginning one hour prior to CTX and completed by 12 hours after the last dose of CTX; 2 mg vincristine intravenously on days 4 and 11; 50 mg/m^2 doxorubicin (Adriamycin) intravenously over 24 hours via central venous catheter on day 4 (given over 48 hours in patients with reduced ejection fractions $<$ 50%); and 40 mg dexamethasone daily either orally or intravenously on days 1 to 4 and days 11 to 14.

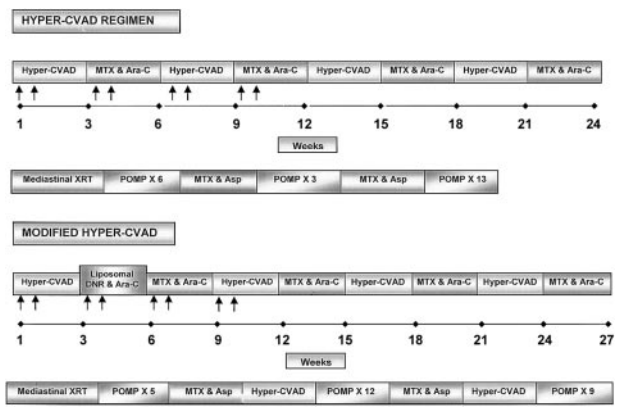

Figure 1. Schema for the hyper-CVAD and modified hyper-CVAD regimens. Arrows indicate intrathecal chemotherapy administrations.

The first course was accompanied by appropriate intravenous hydration and alkalinization (eg, dextrose water or one half normal saline with 75 to 100 milliequivalents of sodium acetate per liter to run at 50 to 100 mL/h) and allopurinol to reduce the incidence of tumor lysis syndrome. Oral sodium bicarbonate supplemented the intravenous formulation on days 1 to 3. Rasburicase could be substituted for allopurinol in cases with high white blood cell count or bulky disease at presentation.

Even courses (2, 4, 6, 8) included high-dose methotrexate and cytarabine: 200 mg/m^2 methotrexate intravenously over 2 hours then 800 mg/m^2 intravenously over 22 hours on day 1; and 3 g/m^2 cytarabine (1 g/m^2 in patients aged 60 or older) over 2 hours every 12 hours for 4 doses on days 2 and 3. Intravenous alkalinization was used to promote excretion of methotrexate in all courses (as for course 1) at a rate of 100 to 125 mL/h. Calcium leucovorin was given at a dose of 50 mg intravenously starting 12 hours after the completion of methotrexate and continued at a dose of 15 mg intravenously every 6 hours for 8 doses until serum methotrexate levels were less than 0.1 μM. An algorithm of additional leucovorin rescue (50 mg IV every 6 hours) was followed if methotrexate blood levels were elevated at the end of infusion (0 hour, confirmed on repeat sample) to more than 20 μM, more than 1 μM at 24 hours, or more than 0.1 μM at 48 hours. Oral acetazolamide was used if the urine pH was less than 7.0.

CNS prophylaxis included alternating intrathecal therapy with 12 mg methotrexate (6 mg only if via Ommaya reservoir) on day 2 and 100 mg cytarabine on days 7 or 8 of each course for a total of either 6 or 8 intrathecal treatments, depending on risk for CNS relapse (based on serum lactate dehydrogenase [LDH] level $>$ 1400 U/L [normal range, 313-618 U/L] and/or proliferative index % $S + G_2M \geq 14\%$).[27] Therapy for active CNS leukemia at presentation included an increase in the frequency of the alternating intrathecal therapy during the induction course to twice weekly until the cerebrospinal fluid (CSF) cell count normalized and cytologic examination was negative for evidence of malignant cells. Intrathecal therapy was then administered weekly for 4 weeks, then according to the prophylactic schedule (2 intrathecals per course) for the remaining courses of intensive chemotherapy. No prophylactic cranial irradiation was given. Therapeutic radiation therapy was given if indicated for CNS disease at presentation (eg, cranial nerve palsies, with 24 to 30 Gy in 10 to 12 fractions directed to the base of the skull).

Course timing and dose modifications were as previously detailed, with subsequent courses of therapy given as soon as the absolute neutrophil count was more than 1×10^9/L (after discontinuation of granulocyte-colony-stimulating factor [G-CSF] for at least 24 hours) and platelet count more than 60×10^9/L. Guidelines for dose reductions included: (1) cytarabine decreased to 1 g/m^2 for age 60 years or older, creatinine more than 176.8 μM (2 mg/dL), or methotrexate level at 0 hour (repeated) more than 20 μM; (2) vincristine to 1 mg for total bilirubin more than 34.2 μM (2 mg/dL), (3) vincristine eliminated if total bilirubin more than 51.3 μM (3 mg/dL) or grades 3 to 4 peripheral neuropathy or ileus; (4) doxorubicin decreased by 50% for bilirubin 34.2 to 51.3 μM (2 to 3 mg/dL), by 75% for bilirubin 51.3 to 85.5 μM (3-5 mg/dL), and eliminated for bilirubin more than 85.5 μM (5 mg/dL); and (5) methotrexate decreased by 50% for calculated creatinine clearance .1667 to .8335 mL/s (10-50 mL/min), with decrease by 25% to 50% for delayed excretion, nephrotoxicity, or grade 3 or greater mucositis with prior courses.

Involved field mediastinal irradiation was recommended for all patients with mediastinal disease. Doses ranged from 30 to 39 Gy given over 4 to 5 weeks. Irradiation was generally administered after completion of the 8 cycles of intensive courses and prior to the initiation of maintenance phase therapy.

Maintenance included 6-mercaptopurine (6-MP), methotrexate, vincristine, and prednisone (POMP) for 24 months. Between 1992 and 1995, oral POMP was given with 50 mg 6-MP orally 3 times daily, 20 mg/m^2 methotrexate orally or intravenously weekly, 2 mg vincristine intravenously monthly, and 200 mg prednisone daily for 5 days monthly, starting with vincristine. Thereafter, intravenous POMP was given with 1 g/m^2 6-MP over one hour daily for 5 days monthly, 10 mg/m^2 methotrexate intravenously over one hour daily for 5 days monthly, and vincristine and prednisone monthly as just described. The 6-MP and methotrexate doses were reduced by 25% (to 750 mg/m^2 and 7.5 mg/m^2, respectively) for

moderate toxicity and by 50% (to 500 mg/m^2 and 5 mg/m^2, respectively) in cases of severe toxicity. The methotrexate dose was usually reduced selectively for mucositis or hepatic dysfunction attributable to the agent.

There were 2 intensification courses administered during the POMP maintenance during months 9 and 12 with 100 mg/m^2 VP-16 intravenously daily on days 1 to 5 and pegylated asparaginase 2500 U/m^2 intravenously on day 1. After July 2000, these intensifications were changed to 100 mg/m^2 methotrexate intravenously on day 1 and 20 000 units L-asparaginase intravenously on day 2, weekly for 4 weeks during months 7 and 11 of maintenance therapy.

Modified hyper-CVAD. From May 2000 until November 2001, patients were treated with the modified hyper-CVAD regimen (Figure 1).[21] Modifications included the addition of a postinduction high-dose anthracycline and cytarabine course (eg, total of 9 instead of 8 induction-consolidation courses) consisting of 150 mg/m^2 liposomal daunorubicin intravenously over 12 hours on days 1 and 2 with 1.5 g/m^2 cytarabine by continuous infusion over 24 hours daily on days 1 and 2. Prednisone (200 mg) was given orally daily for 5 days (days 1-5). The POMP maintenance was extended to 3 years with the early and late intensifications interrupting POMP (cycle of hyper-CVAD followed by or preceding course of methotrexate and L-asparaginase months 6 and 7, and repeated months 18 and 19).

Supportive care

G-CSF (10 μg/kg, rounded) was initiated approximately 24 hours after completion of intensive courses of chemotherapy until absolute neutrophil count (ANC) was higher than 1×10^9/L. Hematologic profiles were obtained at least weekly during the intensive phase of therapy. Appropriate transfusion support was provided with packed red blood cells given for symptomatic and/or severe anemia. Platelet transfusions were given prophylactically for platelet counts lower than 10 to 15×10^9/L or therapeutically for platelet counts lower than 30 to 50×10^9/L with hemorrhage. All blood products were irradiated. Neutropenic febrile episodes generally resulted in hospitalization and initiation of broad spectrum parenteral antibiotics.

During the intensive phase, prophylactic antibiotic therapy included either a quinolone (500 mg ciprofloxacin twice daily or 500 mg levofloxacin daily) or trimethoprim-sulfamethoxazole one double-strength twice daily for antibacterial coverage; 200 mg fluconazole daily for antifungal coverage; and 200 mg acyclovir twice daily (or 500 mg valacyclovir daily) for antiviral coverage. During the maintenance phase, antibiotic prophylaxis consisted of trimethoprim-sulfamethoxazole one double-strength twice daily 2 days a week and 200 mg acyclovir twice daily (or 500 mg valacyclovir daily) to reduce the probability of *Pneumocystis carinii* infection, varicella zoster, or herpes simplex infections.

Response criteria

CR was defined as 5% or fewer blasts in a normocellular or hypercellular marrow with a granulocyte count of 1.0×10^9/L or higher and platelet count of 100×10^9/L or higher. Complete resolution of extramedullary disease was required for CR. Partial response (PR) was defined as at least 50% reduction in nodal and mediastinal disease with clearance of bone marrow and central nervous system disease, if present. Other response outcomes were considered failures. Relapse was defined as disease recurrence at any site after achieving CR. Progression was defined as at least 50% increase in size of residual mediastinal disease.

Statistical considerations

Differences in response rates or pretreatment characteristics among subgroups were analyzed by χ^2 or Fisher exact tests.[28] Survival was measured from the date of initiation of therapy until death from any cause. Progression-free survival (PFS) was measured from the date of best response until documented progression or recurrence. Death in CR was a censored event. Survival and progression-free survival curves were plotted according to the methods of Kaplan and Meier, with differences among them analyzed by the log-rank test.[29] Toxicity was evaluated according to the National Cancer Institute Expanded Common Toxicity Criteria (version 2.0; Bethesda, MD).

Results

Study group

There were 33 patients treated with either the standard (n = 22) or the modified (n = 11) hyper-CVAD regimens. Their characteristics are summarized in Table 1. Their median age was 28 years (range, 17-59 years) and 82% were males. Of 32 patients for whom immunophenotyping was performed, 26 (79%) had T-cell disease. At presentation, 23 patients (70%) had mediastinal involvement, and this was associated with pleural or pericardial effusions in 10 patients (30%). Of the patients, 2 (6%) presented with SVC syndrome, and 3 (9%) with CNS disease. Of the remaining 30 patients without CNS disease (21 treated with hyper-CVAD and 9 treated with modified hyper-CVAD), 11 (37%) were high risk for CNS relapse, 14 (47%) were indeterminate, and 5 (15%) were low risk.

Marrow infiltration less than 25% was identified in 5 patients (15%). Of 33 patients, 24 (73%) underwent karyotypic analysis of the pretreatment bone marrow aspiration. All had diploid karyotype but 2 patients (one with hypodiploid clone and another with hyperdiploid karyotype with additional abnormalities). None harbored translocations or karyotypes typically observed in T-cell LL.

Median hematologic parameters included white blood cell count (WBC) of 6.8×10^9/L (range, 1.9-37.6 $\times 10^9$/L), neutrophil count of 4.68×10^9/L (range, 1.5-30.5 $\times 10^9$/L), hemoglobin of 130 g/L (13.1 g/dL; range, 92-153 g/L [9.2-15.3 g/dL]), and platelet count of 270×10^9/L (range, 129-581 $\times 10^9$/L). There were no significant differences in pretreatment characteristics between the

Table 1. Characteristics of 33 patients with lymphoblastic lymphoma

Characteristic	No. (%)
25 y or older	20 (61)
Male	27 (82)
SVC syndrome	2 (6)
Mediastinal disease	23 (70)
Effusions	
Pleural	10 (30)
Pericardial	3 (9)
Adenopathy	
Cervical	8 (24)
Other	6 (18)
CNS disease at presentation	3 (9)
Skin involvement	3 (9)
Marrow involvement, 6% to 25% blasts	5 (15)
Ann Arbor stage	
I/II	10 (30)
III/IV	23 (70)
Hemoglobin below 120 g/L	10 (30)
LDH IU/L more than twice ULN	8 (24)
β_2 microglobulin, mg % (n = 30)	
3 or higher	3 (9)
B symptoms	10 (30)
Immunophenotype (n = 32)	
T cell	26 (79)
B cell	6 (18)

No patients had clinically significant hepatosplenomegaly at presentation. SVC indicates superior vena cava syndrome; LDH, lactate dehydrogenase; ULN, upper limit normal; and B symptoms, tumor fever higher than 38°C, night sweats, and/or weight loss more than 10%.

2 cohorts treated with the standard or modified hyper-CVAD regimens (data not shown).

Response and outcome

Overall, 30 patients (91%) achieved CR. Among them, 19 patients (63%) achieved CR after 1 course of hyper-CVAD, 5 (17%) after 2 courses, and 6 (20%) after 3 or more courses. All 3 patients with CNS disease responded to intensive intrathecal chemotherapy alone without need for radiation therapy. Achievement of "late" CR was defined as more than 2 courses to achieve that response. Of the 8 patients who were classified as such, 3 had insufficient radiographic imaging (eg, continual improvement on routine imaging but absence of definitive tomography imaging documenting CR until 2-3 additional courses had been administered).

There were 3 patients (9%) who did not achieve CR with induction-consolidation, mainly related to residual mediastinal masses 2 cm or larger as assessed by serial computed tomographic imaging. These patients were classified as partial responders since it could not be determined whether viable tumor remained (gallium imaging was not performed in all cases). Of these patients, 2 progressed at 8 and 12 months from start of therapy. Disease characteristics are detailed in Table 2 (patient nos. 9 and 10). The third 37-year-old male patient consolidated subsequently with mediastinal irradiation (no other sites of disease at presentation) remained without evidence of disease progression at 29+ months.

Of 23 patients with mediastinal disease at presentation, 17 (74%) received consolidative mediastinal irradiation following the 8 cycles of induction-consolidation. Owing to refusal or comorbid medical conditions, 3 patients (13%) did not receive radiation therapy. Mediastinal relapse (not isolated) occurred in 2 (12%) of 17 patients who had mediastinal irradiation, and in 1 (33%) of 3 patients who did not. Owing to early disease progression prior to completion of the consolidation courses of chemotherapy, 3 patients did not receive the planned local therapy.

Treatment delivery was appropriate for this younger age group. All patients remaining in complete remission completed the 8 cycles (hyper-CVAD) or 9 cycles (modified hyper-CVAD) of induction-consolidation chemotherapy. Maintenance therapy was commenced upon completion of the last course of therapy (unless deferred until completion of radiation therapy). Intensification cycles were administered according to the schema outlined. None of the patients underwent allogeneic or autologous stem cell transplantation (SCT) as consolidation or intensification in first complete remission.

Three patients (9%) died while still in continuous CR. One HIV-negative patient developed multiorganism pneumonia with *Pneumocystis carinii* and cytomegalovirus confirmed by bronchoscopy and died of respiratory failure at 7 months from start of therapy. A second patient died at 20 months during maintenance therapy of presumed herpes encephalitis. The third patient developed acute myelogenous leukemia (AML) at 35 months, achieving CR initially with frontline high-dose cytarabine-based therapy, but relapsing after 8 months with failure to salvage therapy including allogeneic SCT.

Within a median of 13 months from the start of therapy (range, 5-37 months), 10 patients (30%) relapsed or progressed. Of these patients, 2 achieved a second CR, the remainder dying of disease (see "Salvage therapy," below). With a median follow-up time of 48 months (range, 8-110+ months), 22 (67%) patients remained alive without evidence of disease (Figure 2), with 20 (61%) of the 33 treated patients in continuous CR from the initial regimen.

Details of the patients who relapsed are provided in Table 2. Of these patients, 2 (nos. 2, 6) presented with concurrent features of myeloproliferative syndrome and eosinophilia; however, the t(8; 13) karyotype was not identified in either case.[30] There were 5 patients who relapsed with mediastinal disease (2 with isolated relapse), 3 with CNS disease (1 isolated relapse), and 3 with marrow disease (1 isolated). There were 4 patients who had involvement of multiple sites at the time of relapse. None of the patients with bone marrow involvement at start of therapy relapsed.

Analysis of PFS and overall survival by pretreatment prognostic factors and by treatment regimen is shown in Tables 3 and 4, respectively. CNS disease at presentation appeared to predict for shorter PFS ($P = .02$); however, no other factors appeared to predict outcome. Those with B-cell immunophenotype appeared to fare better than the T-cell counterparts, although this did not reach statistical significance owing to the small number of patients in this historically favorable group. Although the numbers were small, outcome appeared to be inferior for the modified hyper-CVAD regimen compared with standard hyper-CVAD (Table 4).

Toxicity

Toxicity profile of the hyper-CVAD regimens was as expected and similar to prior reports (Table 5).[20] No induction mortality was observed. There was no correlation between dose modifications required for toxicities and outcome (data not shown).

Table 2. Pattern of relapse/progression in lymphoblastic lymphoma

Patient no.	Age, y	Sex	Regimen	Mediastinal XRT?	Response	Months to relapse or progression*	Initial sites of disease	Sites of relapse
1	29	F	M-HCVAD	N†	CR	5	M, pleural	M
2	53	M	M-HCVAD	N†	CR	8	M, nodes, CNS	Nodes
3	37	M	HCVAD	Y	CR	12	M, nodes	BM, CNS
4	27	M	HCVAD	Y	CR	14	M	BM
5	28	M	HCVAD	N	CR	22	M, pleural	M
6	33	M	HCVAD	N	CR	23	Nodes	Nodes
7	23	F	HCVAD	Y	CR	27	M, nodes	M, BM
8	27	M	HCVAD	Y	CR	37	M, nodes	CNS
9	23	M	M-HCVAD	N†	PR	8	M, CNS, pleural, pericardial	M, CNS
10	44	M	M-HCVAD	Y	PR	12	M, pleural	M, pleural, BM

XRT indicates radiation therapy; M-HCVAD, modified hyper-CVAD; CR, complete remission; PR, partial response; M, mediastinum; pleural, pleural effusions; CNS, central nervous system; and BM, bone marrow.

*From start of therapy.

†Progression during intensive phase of chemotherapy prior to planned mediastinal XRT.

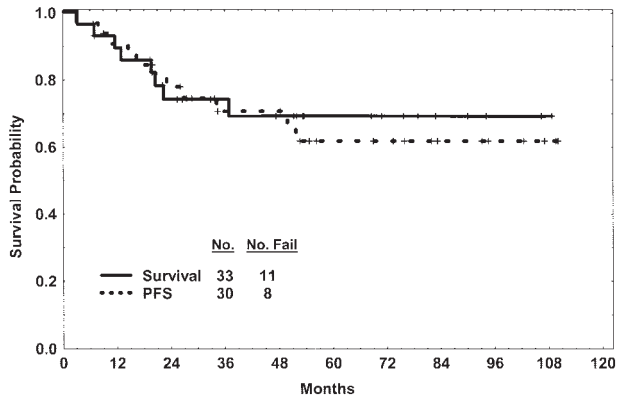

Figure 2. Progression-free and overall survival of the entire study group treated with either hyper-CVAD or modified hyper-CVAD. PFS indicates progression-free survival.

Salvage therapy

All but 1 of the 10 patients who relapsed underwent salvage therapy; 4 were retreated with the hyper-CVAD regimen or its variants and 2 of them achieved a second CR. One of these responders underwent matched unrelated donor (MUD) SCT and remained alive without disease at 5+ years. The other responder underwent autologous intensification, but developed CNS relapse with systemic progression and succumbed to complications of disease. One failure to hyper-CVAD underwent allogeneic SCT with active disease and remained alive at 4+ years after achievement of CR. The other failure underwent matched related sibling (MRD) SCT, but subsequently relapsed and failed further salvage therapy attempts.

There were 5 other patients treated with MOAD (methotrexate, vincristine, asparaginase, and dexamethasone). Of the 3 responders (2 CRs, 1 PR), 2 subsequently underwent allogeneic SCT and succumbed to infectious complications or graft-versus-host disease. The other MOAD failures subsequently died of leukemia-related complications after multiple alternative salvage attempts.

Discussion

The results of the hyper-CVAD regimen in LL were very encouraging. Overall, 91% of patients achieved CR, and the estimated 3-year overall survival rate was 70%, with a PFS rate of 66% (Figure 1). These results compare favorably with previously published studies of ALL-type regimens in which CR rates ranged from 70% to 80% and DFS rates from 30% to 50%.[2,11-16] Hoelzer et al[31] recently reported on the German experience with the Berlin-Frankfurt-Muenster (BFM) regimens for ALL as applied to patients with LL. Among 50 patients with T-cell LL (including 3 patients with T-cell ALL presenting with mediastinal disease with marrow involvement > 25%), 45 (93%) were evaluable for response and outcome after treatment. Their median age was 25 years (range, 15-61 years), similar to that of our group (28 years). Distribution of other patient characteristics was similar to those included in our study, except for confinement of the analysis to patients with T-cell immunophenotype. Overall, 42 (93%) of 45 evaluable patients achieved CR with the BFM ALL regimens. Of the patients, 4 had one prior course of therapy. The length of follow-up between the 2 studies is similar, with a median follow-up of 45 months (range, 12-91 months) for Hoelzer et al[31] and 48 months (range, 8-110 months) for our study. The estimated 5-year durable remission and survival rates were 65% and 51%, respectively, for those patients treated with the BFM regimens, and 62% and 67%, respectively, for the T-cell subset reported in our study (all previously untreated).

Factors influencing outcome in LL in series reporting results with lymphoma-type regimens have included older age, leukocytosis, anemia, presence of peripheral lymphoblasts, high serum LDH levels, and longer time to achieve CR; however, these parameters have not been reproducible or useful for prognostication.[1-3,7] In the study of Hoelzer et al,[31] no prognostic factors were identified to predict outcome, although the combination of a delayed response and high serum LDH predicted for worse remission duration (durable remission rates 73% versus 43%; $P = .09$). In our study, we identified only CNS disease at presentation (no CNS disease was observed in the study of Hoelzer et al[31]) and lack of achievement of CR to have prognostic import. There appeared to be

Table 3. Prognostic factors for PFS and survival

Parameter	No.	Estimated 3-y rate (%) PFS	*P*	Survival	*P*
Overall	33	66	—	70	—
Age					
Younger than 30 y	19	72	NS	77	NS
30 y or older	14	66		64	
Sex					
Male	27	72	NS	73	NS
Female	6	63		56	
Ann Arbor stage					
I/II	10	86	NS	76	NS
III/IV	23	70		68	
Mediastinal disease					
Yes	23	59	NS	67	NS
No	10	83		77	
CNS disease					
Yes	3	33	.02	33	NS
No	30	74		74	
Adenopathy					
Yes	11	68	NS	72	NS
No	22	72		71	
Marrow involvement					
6%-25%					
Yes	5	100	NS	60	NS
No	28	72		75	
Hemoglobin					
Lower than 120 g/L	10	71	NS	55	NS
120 g/L or higher	23	67		77	
Platelet count					
100×10^9/L to 450×10^9/L	30	67	NS	67	NS
Higher than 450×10^9/L	3	100		100	
LDH (IU/L)					
2 × ULN or less	25	88	NS	73	NS
More than 2 × ULN	8	65		70	
B symptoms					
Yes	23	69	NS	70	NS
No	10	71		71	
β_2 microglobulin, (n = 30)					
Lower than 3 mg %	27	50	NS	67	NS
3 mg % or higher	3	76		76	
Immunophenotype (n = 32)					
T cell	26	62	.09	67	NS
B cell	6	100		80	
Courses to response					
1	19	81	NS	73	NS
2 or more	14	67		68	

NS indicates not significant; LDH, lactate dehydrogenase; ULN, upper limit normal; and —, not applicable. Courses to respond were 3 (n = 3), 4 (n = 2), or other (5, 8, or 10 courses).

Table 4. Outcome with hyper-CVAD compared with modified hyper-CVAD

Parameter	Hyper-CVAD	Modified hyper-CVAD	*P*
No. treated	22	11	—
No. response (%)	22 (100)	11 (100)	NS
No. CR (%)	22 (100)	8 (73)*	.01
Estimated 3-y rates (%)			
Survival	83	49	.01
Response duration	77	62	

No significant differences in pretreatment characteristics by cohort (data not shown). — indicates not applicable; NS, not significant.

*Others with partial responses.

no difference in outcome by number of courses to achieve CR, although timing of the radiographic assessments could have influenced this parameter.

In our study, the incidence of isolated CNS relapse was low (3%). This suggests that the combination of high-dose systemic chemotherapy and appropriate intrathecal CNS chemotherapy (usually 8 intrathecal injections in our study) was adequate CNS prophylaxis, thus alleviating the need for, and potential complications of, prophylactic cranial irradiation for LL. In the study of Hoelzer et al,[31] none of the 45 patients had CNS disease at presentation. CNS relapse occurred in only 1 (2%) of the 45 patients treated with CNS prophylaxis consisting of 5 intrathecal chemotherapy applications and cranial irradiation (24 Gy).

The role of consolidative mediastinal radiation therapy in adult LL is less well defined in the setting of ALL-type therapy. Consolidative mediastinal irradiation has not been of proven benefit in childhood LL. An early randomized prospective clinical trial of mediastinal radiation therapy in childhood LL demonstrated increased toxicity without clinical benefit.[32] Low-dose irradiation (15 Gy) did not improve local mediastinal control; a local failure rate of 54% was observed in children with LL treated with either the LSA2L2 or ADCOMP chemotherapy regimens.[33] The childhood experience using a similar BFM regimen to that of Hoelzer et al[31] did not include consolidation radiation therapy, but used intensive high-dose methotrexate (5 g/m^2), which cannot probably be delivered to adults without significant nephrotoxicity.[34] This regimen was associated with a significantly lower rate of mediastinal relapse (7%).[34] In adult LL, review of outcome with consolidative mediastinal radiation therapy given after conventional (VAD)[35] and intensive (hyper-CVAD) ALL regimens appeared to reduce the incidence of locoregional relapse.[36]

In the study of Hoelzer et al,[31] mediastinal radiation therapy (24 Gy) was recommended in all patients, and comprised only the anatomic mediastinum, not the original extent of mediastinal tumor. Mediastinal radiation therapy was implemented in 32 (84%) of 41 of patients presenting with mediastinal disease. Despite this strategy, of the 15 patients who relapsed, 7 (47%) had mediastinal relapse despite prior radiation therapy.[31] This high incidence of mediastinal relapse led these investigators to propose a higher radiation dose (36 Gy instead of 24 Gy) for future studies. In our study, patients who received mediastinal irradiation (30 to 39 Gy) had lower incidences of mediastinal relapse, although small numbers make definitive comparisons difficult. Only 2 (12%) of 17 patients treated with consolidative irradiation relapsed in the mediastinum (and at other sites). Early progression in the mediastinum occurred prior to the use of consolidative irradiation in 3 (13%) of the 23 patients for whom radiation therapy was planned. These studies suggest a possible role for appropriate dose consolidative mediastinal irradiation in adults. A larger randomized prospective clinical trial is needed in adults to address this issue.

Based on their observed outcome with the BFM regimen used for adult LL, Hoelzer et al[31] plan to incorporate intensive fractionated cyclophosphamide, high-dose cytarabine, and extended maintenance therapy for future studies in an attempt to improve the DFS. These components are already present in the hyper-CVAD regimen, perhaps accounting for the outcome observed in our study (estimated 3-year survival and PFS rates of 83% and 77%, respectively, with the standard hyper-CVAD regimen).

In our study, use of early anthracycline intensification did not appear to add benefit for the few patients treated with the modified hyper-CVAD regimen. In keeping with this finding, a recent report of 91 adults with LL demonstrated that outcome with high-dose anthracycline NHL regimens was inferior to conventional NHL regimens, with 5-year survival and event-free survival rates of 32% and 22%, respectively.[37] The inferior results observed with other reports of NHL regimens underscore the need to treat LL with typical ALL-type regimens, incorporating central nervous system prophylaxis and consolidative mediastinal irradiation for locoregional control.

Explanations for the inferior outcome observed with the modified hyper-CVAD regimen may include differences in disease and/or patient characteristics (eg, latent variables) between the 2 treatment groups (hyper-CVAD versus modified hyper-CVAD) not detectable by statistical analysis owing to small patient numbers.

Table 5. Toxicity with hyper-CVAD or modified hyper-CVAD for LL (n = 33)

Parameter	No.	Percent of patients	
		Grades 1-2	Grades 3-4
Infections during induction (71 courses)*			
FUO	13	—	13
Sepsis	8	—	8
Pneumonia	2	—	2
Fungal	1	—	1
Infections during consolidation (131 courses)			
FUO	32	—	32
Sepsis	9	—	9
Pneumonia	8	—	8
Fungal	2	—	2
Other	5	—	5
Gastrointestinal			
Stomatitis	15	33	12
Nausea/vomiting	6	15	3
Ileus	1	0	3
Renal			
Increase in creatinine	1	3	0
Neuromuscular			
Peripheral neuropathy	5	9	3
Cardiovascular			
Pericarditis	1	0	3
Hepatic			
Increase in bilirubin	3	6	3
Increase in transaminases	6	6	12
Pancreatitis	1	0	3
Dermatologic			
Rash	1	0	3

Other includes cytomegalovirus pneumonia, *Pneumocystis carinii* pneumonia, disseminated herpes zoster, and herpetic encephalitis.

*No. of episodes per course until CR.

†All episodes of infections listed were grade 3 or greater.

FUO indicates fever of unknown origin; —, not applicable.

There were no induction deaths with either treatment regimen. No significant differences in toxicity profiles of the 2 regimens were apparent. The recurrence or progression rate was similar for the 2 groups (27% versus 37%, P = NS); however, all patients treated with hyper-CVAD achieved CR, whereas the best response for 3 patients treated with the modified hyper-CVAD was PR (100% versus 73%, $P = .01$), suggesting perhaps that early consolidation with high-dose methotrexate and cytarabine may be beneficial for long-term progression-free survival. Further clinical trials will be needed to delineate optimal dose and components of the chemotherapy regimens, dose intensity, timing of mediastinal irradiation, and duration of maintenance therapy.

In summary, our experience with the hyper-CVAD regimen in LL was very encouraging. Modifications could include earlier mediastinal irradiation for slow responders and use of alternative intrathecal chemotherapy agents such as liposomal cytarabine to reduce the incidence of CNS relapse. Intensification of the hyper-CVAD regimen with L-asparaginase during induction-consolidation will be explored. Concurrent administration of hyper-CVAD and alemtuzumab, a monoclonal antibody to CD52 with high expression in T-cell malignancies, is under investigation in the salvage setting.[38] Nelarabine, a nucleoside analog with activity in previously treated T-cell acute ALL, LL, and other leukemias, should be incorporated into frontline therapy, perhaps for slow responders or those with other high-risk features.[39] The role of SCT in first remission will depend on identifying those patients at high risk for disease progression or recurrence, given the favorable outcome with ALL regimens in the absence of such intensification. Future studies should focus on identifying these poor prognostic groups by gene expression profiling or other biologic markers, including assessments for minimal residual disease, in order to implement risk-oriented approaches.

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