Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone and Highly Active Antiretroviral Therapy for Patients with Acquired Immunodeficiency Syndrome-Related Burkitt Lymphoma/Leukemia

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BACKGROUND. Patients with acquired immunodeficiency syndrome (AIDS)-associated lymphoma/leukemia have a poor prognosis and are frequently treated with low-intensity therapy. The authors investigated the feasibility and efficacy of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a dose-intensive chemotherapy regimen, in patients with AIDS-associated Burkitt lymphoma/leukemia, as well as the possible impact of highly active antiretroviral therapy (HAART) in these patients.

METHODS. Thirteen patients with AIDS-associated Burkitt lymphoma (six patients) or leukemia (acute lymphoblastic leukemia; seven patients) were treated with hyper-CVAD alternating with high-dose methotrexate and ara-C for a total of eight cycles. Nine patients received HAART from the start of induction chemotherapy (seven patients) or later in the course of chemotherapy (two patients). The median patient age was 43 years (range, 32–55). Nine patients were diagnosed with human immunodeficiency virus (HIV) infection at the time of diagnosis of Burkitt lymphoma/leukemia; the other 4 patients had been diagnosed with HIV infection for a median of 37 months (range, 18–137) prior to the diagnosis of Burkitt lymphoma/leukemia. The median absolute CD4 count from the 9 patients with evaluable counts was 77 cells/μL (range, 9–544); only one patient had a count > 200/μL.

RESULTS. Twelve patients (92%) achieved a complete remission (CR) and one achieved a partial response (PR). Eight patients continued in CR after a median of 31 months (range, 7–45) at the time of writing. Five patients were alive and in CR over two years later. The median survival was 12 months, with 48% of patients alive after 2 years. Six of seven patients who received HAART from the start of chemotherapy were alive and in CR after a median of 29 months (range, 7–45). The four patients who did not receive HAART died. The regimen was universally myelosuppressive, but the toxicity profiles, recoveries from myelosuppression, and incidences of infectious complications were similar to that of non-HIV patients with Burkitt lymphoma/leukemia treated with the same regimen.

CONCLUSIONS. Hyper-CVAD is an effective regimen for patients with AIDS-associated Burkitt lymphoma/leukemia, with acceptable toxicity. The combination of hyper-CVAD and HAART is associated with long-term survival in patients with the two diseases, which, until recently, were both considered invariably fatal and almost futile to treat medically. Cancer 2002;94:1492-9.

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KEYWORDS: acquired immunodeficiency syndrome, Burkitt lymphoma/leukemia, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), highly active antiretroviral therapy.
Patients with human immunodeficiency virus (HIV) infection have an increased risk of developing non-Hodgkin lymphomas (NHL) regardless of the risk-group for HIV. The risk of developing NHL among HIV-infected individuals is 150- to 250-fold that of the general population. Several NHLs are acquired immunodeficiency syndrome (AIDS) defining illnesses, including high-grade immunoblastic or diffuse large-cell lymphoma, primary NHL of the central nervous system (CNS), and small noncleaved cell NHL (Burkitt, Burkitt-like, or non-Burkitt). While only a small percentage of patients have NHL as their initial AIDS-defining diagnosis, the risk increases over time, and NHL accounts for approximately 16% of deaths among patients with AIDS. The risk might increase with worsening immunosuppression, and NHL has been reported in 30% of patients within 3 years of reaching a CD4+ lymphocyte count of \( < 50 \times 10^9/L \). Most NHLs diagnosed in patients with AIDS are of high-grade histology, with immunoblastic lymphoma being the most common (relative risk \( \times 627 \) compared to the general population).

Burkitt or Burkitt-like lymphomas represent 25% to 40% of HIV-associated lymphomas, with the risk among AIDS patients 200 to 1000 times higher than that of the general population. In contrast to other HIV-associated NHLs, Burkitt or Burkitt-like lymphomas may develop earlier during the natural course of HIV infection, when CD4+ lymphocyte counts are relatively high. The translocation of \((t(8;14)(q24;q32)\) is found in Burkitt lymphoma patients both with and without HIV infection. Interestingly, this translocation has been detected in up to 10% of HIV-seropositive but otherwise asymptomatic homosexual men.

Epstein-Barr virus can be identified in only 30-40% of HIV-associated Burkitt lymphomas. The prognosis of patients with HIV-associated Burkitt lymphoma is very poor. Only 40–50% of patients achieve a complete remission (CR), and the median survival is less than one year, with 5–7% long-term survival.

Significant progress has been made in Burkitt lymphoma/leukemia not associated with HIV in recent years, with CR rates of \( \geq 90\% \) and long-term event-free survival rates of 55-85%. The use of highly active antiretroviral therapy (HAART) has changed the long-term outlook for patients with HIV infection, improving CD4 lymphocyte counts, decreasing the incidences of AIDS-associated opportunistic infections, and resulting in prolonged survival.

The use of HAART has led to a decrease in the incidence of Kaposi sarcoma and possibly primary CNS lymphoma, but not other non-Hodgkin lymphomas.

In the current study we report the use of the hyper-CVAD regimen for patients with HIV-associated Burkitt leukemia/lymphoma. Both these conditions were thought to be invariably fatal prior to the advent of effective therapy for Burkitt lymphoma and HIV. Thus, it is significant that the addition of HAART to hyper-CVAD was associated with a high probability of long-term disease-free survival.

**Patients and Methods**

From October 1995 to August 2000, thirteen adult patients with newly diagnosed, previously untreated mature B-cell acute lymphoblastic leukemia (ALL-L3, Burkitt leukemia) or small noncleaved cell lymphoma (Burkitt lymphoma) were referred for treatment to The University of Texas M.D. Anderson Cancer Center. The diagnosis of Burkitt lymphoma or leukemia was established as previously described. Eligibility criteria included age \( \geq 15 \) years, biopsy-proven diagnosis of Burkitt lymphoma/leukemia, no prior therapy for Burkitt leukemia/lymphoma, and documented HIV infection. There was no restriction by performance status, older age, or organ dysfunction. Patients were eligible regardless of CD4 count, use of anti-retroviral therapy, or history of other AIDS-defining or associated conditions. Informed consent was obtained according to institutional guidelines.

At the time of referral, patients had their history taken, and also underwent a physical exam, bone marrow aspiration and biopsy, lumbar puncture for cerebrospinal fluid (CSF) cytologic analysis, chest radiograph, and chest, abdomen, and pelvis computerized axial tomography scans. Laboratory evaluations included complete blood counts, differential and platelet counts, sequential multiple analysis with liver and renal function studies, coagulation profiles, CD4 lymphocyte counts, and HIV viral load counts.

After completion of induction therapy, assessments were performed periodically with physical examinations, laboratory evaluations (including bone marrow aspirations), and radiography every two to three months for the first year, every four to six months for the second year, every six months for the third year, and annually thereafter.

**Therapy**

Hyper-CVAD was administered as previously described. Briefly, eight courses of alternating intensive chemotherapy were given. Odd-numbered courses (1, 3, 5, and 7) were hyper-CVAD: 1) hyperfractionated cyclophosphamide (CTX), 300 mg/m² intravenously (i.v.) over 2 hours every 12 hours for six doses on Days 1–3 (with mesna, 600 mg/m²/d i.v. via continuous infusion on Days 1–3 beginning 1 hour prior to CTX and completed by 12 hours after the last dose of CTX); 2) vincristine, 2 mg i.v. on Days 4 and 11; 3) doxorubicin, 50 mg/m² i.v. over 2
hours on Day 4; and 4) dexamethasone, 40 mg daily either orally or i.v. on Days 1–4 and Days 11–14. During the first course, allopurinol was given together with intravenous hydration and alkalinization to reduce the complications from tumor lysis. Even-numbered courses (2, 4, 6, and 8) consisted of methotrexate (MTX) and ara-C: MTX, 1 gm/m² i.v. over 24 hours on Day 1, and ara-C, 3 gm/m² over 2 hours every 12 hours for four doses on Days 2 and 3. Calcium leucovorin was given at a dose of 50 mg i.v. starting 12 hours after the completion of MTX and continued at a dose of 15 mg i.v. every 6 hours for 8 doses until MTX blood levels were less than 0.1 μM. Oral sodium bicarbonate supplemented the intravenous formulation on Days 1–3. Oral acetzolamide was utilized if the urine pH was < 7.0. Beginning in March 2000, the protocol was modified to include rituximab, 375 mg/m² i.v. on Days 1 and 11 of Courses 1 and 3 and on Days 1 and 8 of Courses 2 and 4.

Standard dose reductions included: 1) ara-C to 1 g/m² for age ≥ 60 years, creatinine > 2 g/dL, or MTX level at 0 hour > 20 μM; 2) vincristine to 1 mg for total bilirubin > 2 g/dL; 3) doxorubicin by 25% for bilirubin 2-3 g/dL, by 50% for bilirubin 3-4 g/dL, and by 75% for bilirubin above 4 g/dL; and 4) MTX by 50% for creatinine > 2 g/dL, by 75% for creatinine > 3 g/dL; or by 50-75% for delayed excretion and/or nephrotoxicity with a previous course (the degree of reduction dependent on the severity).

We initiated G-CSF (10 μg/kg/day subcutaneously) at least 24 hours after chemotherapy was completed and continued until the white blood cell (WBC) count was ≥ 3.0 × 10⁹/L. Subsequent courses were initiated when the WBC count was ≥ 3.0 × 10⁹/L and the platelet count was ≥ 60 × 10⁹/L. Courses were given every 21 days or earlier if count recovery was noted (but at least 14 days from the last course). No maintenance therapy was administered after the eight cycles were completed.

Central nervous system prophylaxis included alternating intrathecal administrations of 12 mg of MTX (6 mg via Ommaya reservoir) on Day 2 and 100 mg of ara-C on Day 7 of each course for all 8 courses (16 intrathecal chemotherapy administrations) as previously described. Patients with documented CNS involvement received intrathecal chemotherapy twice weekly during induction until the CSF cell count was normalized and the cytologic examination was negative; the prophylactic schema described above was then resumed. No prophylactic cranial irradiation (XRT) was administered, although therapeutic XRT to the base of the skull was used for patients with cranial nerve palsy.

Supportive Care

All patients received antibiotic prophylaxis with a quinolone, anti-fungal prophylaxis with fluconazole, and antiviral prophylaxis with acyclovir or valacyclovir. In addition, patients received PCP prophylaxis with trimethoprim-sulfamethoxazole during chemotherapy. Ganciclovir for cytomegalovirus (CMV) prophylaxis and azithromycin for Mycobacterium avium prophylaxis were used at the discretion of the treating physician. Hematologic profiles were obtained at least biweekly; transfusion support was provided as clinically indicated with irradiated blood products.

Antiretroviral therapy with triple drug combination was recommended to all patients upon diagnosis of Burkitt lymphoma/leukemia. Therapy was administered following the recommendations of the AIDS Society. Patients who were already receiving antiretroviral therapy prior to diagnosis of Burkitt lymphoma/leukemia continued their therapy; otherwise, therapy was to start during the first chemotherapy course. The combinations used included: stavudine (d4T), lamivudine (3TC) and indinavir (six patients); stavudine, lamivudine, and ritonavir (one patient); stavudine, lamivudine, and nelfinavir (one patient); and lamivudine, efavirenz, and amprenavir (one patient).

Response Criteria

Complete remission (CR) was defined as ≤ 5% blasts in a normocellular or hypercellular marrow with a granulocyte count > 1.0 × 10⁹/L and platelet count > 100 × 10⁹/L. Complete resolution of extramedullary disease was required for a CR. Induction death was defined as death after start of therapy (usually within four weeks) without meeting the definition of CR or resistant disease. Resistant disease was diagnosed when a patient survived the induction treatment but did not achieve a CR. Relapse was defined as disease recurrence at any site after achieving CR. Toxicity was evaluated according to the National Cancer Institute criteria.

Statistical Methods

Survival was measured from the date therapy was initiated until death from any cause. Complete remission duration was measured from the date of CR until documented relapse. Toxic deaths in CR were considered as failures at the time of death on the remission duration curves; thus CR duration and disease-free survival for patients achieving CR were interchangeable in this analysis. A cut-off date of February 28, 2000, was established for analyzing the data for this report. Survival and remission duration curves were
plotted according to the methods of Kaplan and Meier.24

RESULTS

Thirteen patients were treated; their clinical characteristics are presented in Table 1. Twelve patients were males, and the median age was 43 years (range, 32–55 years). Nine patients were diagnosed with HIV infection at the time of diagnosis of Burkitt lymphoma/leukemia; the other 4 patients had been diagnosed with HIV infection for a median of 37 months (range, 18–137), but only 2 had a diagnosis of AIDS. Seven patients (50%) were classified as having acute lymphoblastic leukemia L3 (ALL-L3) on the basis of bone marrow blasts ≥ 30%. Among patients with Burkitt lymphoma, two had Ann Arbor Stage II and four patients had Stage IV disease (liver, three patients; bone marrow, one patient; and skin, one patient). Three patients with ALL-L3 had CNS involvement at diagnosis; gastrointestinal and liver involvement were present in one patient each. Seven of ten patients with evaluable cytogenetic analysis had the typical Burkitt karyotype, including t(8;14) (five patients), t(2;8) (one patient), and t(8;22) (one patient); four of these patients had additional chromosomal abnormalities. Three patients had normal diploid cytogenetics (none of the three had bone marrow involvement). Three patients had active infections at the time of diagnosis: one episode each of thrush, gingival abscess, and pneumonia of unknown pathogen. Five patients had positive CMV antigenemia at the time of diagnosis; two had positive serology for hepatitis C, and one for hepatitis B surface antigen. Four patients (31%) had performance status ≥ 3, and two patients required hemodialysis at the time of diagnosis. Among the nine patients with available information, the median CD4 count was 77/L (range, 9–544/L), and only one patient had a CD4 count ≥ 200/L. The HIV viral load was measured in eight patients at the time of diagnosis, with a median of 32,000 copies/mL (range, 690–674,200 copies/mL).

Twelve patients (92%) achieved CR and one patient (ALL with splenomegaly, lymphadenopathy, and CNS and liver involvement at diagnosis) had a partial remission (PR) (persistent splenomegaly, with no other evidence of disease). The CRs occurred after the first cycle of chemotherapy in 10 patients; one patient required 2 cycles to achieve CR, and one patient did not have documented CR until after the fourth cycle. Six of the seven patients with cytogenetic abnormalities at the time of diagnosis became diploid at the time of CR; one patient had no analyzable metaphases at the time of CR. Three additional patients with unavailable cytogenetics at diagnosis were diploid at the time of CR.

Four (33%) of the 12 patients achieving CR relapsed after a median of 4 months (range, 2–6 months). One patient died in CR, and, at the time of writing, eight patients continue in CR after a median of 31 months (range, 7–45). The median overall CR duration was not reached; at time of writing, 52% of patients remain alive and in CR after two years (Fig. 1). The median survival for the study group was 12 months, with 48% of patients alive after 2 years (Fig. 2).

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TABLE 1

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HIV: human immunodeficiency virus; ALL: acute lymphoblastic leukemia; IVDU: intravenous drug use; AIDS: acquired immunodeficiency syndrome.

Nine patients had Burkitt’s lymphoma/leukemia as their AIDS-defining condition. B2M: β2 microglobulin; LDH: lactic dehydrogenase; BM: bone marrow.

FIGURE 1. Disease-free survival among 12 patients achieving complete remission (CR).
patient died in CR after two months from a fungal pneumonia. The median survival was not reached for patients achieving a CR.

Nine patients (64%) received HAART: 7 patients (50%) started their therapy before the diagnosis of Burkitt lymphoma/leukemia (2 patients) or during the first course of chemotherapy (5 patients); one patient started HAART 4 months from diagnosis of Burkitt lymphoma/leukemia, while receiving the fifth cycle of chemotherapy; and one patient started after completion of all chemotherapy. Four patients did not receive anti-HIV therapy because of financial reasons or refusal. The viral load became undetectable during chemotherapy in seven of the nine patients who received HAART; in two patients viral loads later increased associated with discontinuation of HAART while in CR from the Burkitt lymphoma/leukemia (one patient) or relapse from Burkitt lymphoma/leukemia (one patient). Two other patients had a 1.5–2 log reduction in viral load at their last measurement. Among the seven patients who received HAART throughout all their chemotherapy, six remain alive and in CR for a median of 29 months (range, 7–45) at the time of writing. Two patients started HAART later; one patient who started HAART late into chemotherapy relapsed two months later and eventually died of progressive disease, and the patient who started after all chemotherapy was completed was alive and in CR after 33 months at the time of writing. The four patients who did not receive HAART died, one in CR and three with progressive disease (two relapsed, one achieved only PR).

Dose Delivery and Toxicity
The median number of cycles of chemotherapy delivered was six (range, three to eight). Six patients did not complete the planned eight cycles because of relapse while on therapy (four patients, who received four, four, six, and seven cycles, respectively), progression of disease (one patient; PR only, three cycles), or death in CR (one patient; three cycles). All of these patients died. The seven surviving patients received a median of seven cycles (range, five to eight): three patients completed eight cycles; one patient stopped chemotherapy after five cycles because of social circumstances, and two after seven cycles because of prolonged thrombocytopenia; and one patient received five cycles and completed chemotherapy and is in CR at the time of press. Grade 3 to 4 myelosuppression was universal and all patients required multiple red blood cell and platelet transfusions throughout their chemotherapy. The median time to recovery of neutrophils to $\geq 0.5 \times 10^9/L$ was 18 days (range, 14-20 days) and platelets to $\geq 60 \times 10^9/L$ was 17.5 days (range, 14-28 days) for Course 1. Similar results were obtained with subsequent courses, and this is reflected in the time to administration of subsequent cycles as shown in Figure 3. Although the number of evaluable observations decreases with later courses, a non-statistically significant trend was observed for more delays after even-numbered (i.e., methotrexate and cytarabine) courses.

Dose modifications were required in 16 of 75 administered cycles (21%); 11 of these were even-numbered cycles (i.e., methotrexate and cytarabine), with dose reductions in methotrexate and/or cytarabine of 33% to 66% (median 50%) due to delayed methotrexate clearance and/or prolonged myelosuppression. Five odd-numbered cycles (i.e., hyper-CVAD) required dose adjustment of vincristine (eliminated in all five
instances due to neurotoxicity) or doxorubicin (one patient, due to elevated bilirubin).

Twenty-six cycles (35%) were complicated by fever or infections. These included 14 episodes of fever of unknown pathogens, 7 episodes of pneumonia (1 documented *Candida krusei*, 1 suspected fungal, 5 unknown pathogens), 2 episodes of catheter-related sepsis, and one episode each of *Xanthomonas maltophilia* sepsis, CMV retinitis, and Fusarium (skin). Two of these episodes were fatal (*C. krusei* pneumonia, death in CR, and *X. maltophilia* sepsis, death in PR). In addition, six patients developed CMV antigenemia (i.e., ≥ two positive cells) during chemotherapy; four of these patients had had a positive test at the time of diagnosis. Only one of these patients had evidence of CMV-associated infection (retinitis).

**DISCUSSION**

The treatment of patients with AIDS-associated non-Hodgkin lymphoma has been challenging. The response rate using conventional therapy has been low and the frequency of complicating opportunistic infections high. In the current study we report on the use of hyper-CVAD in 13 patients with AIDS-associated Burkitt lymphoma/leukemia. The CR rate was 92%, with a median survival of 12 months. The median CR duration had not been reached, with a projected 52% of patients alive and in CR after 2 years at the time of writing. The median survival for patients achieving CR was not reached. Five patients (38%) were in remission for more than 2 years. Since relapses in Burkitt leukemia/lymphoma are very rare after two years, these patients are likely to be cured of this malignancy.

The hyper-CVAD regimen was modeled after Murphy et al. for children with Burkitt type or mature B-cell ALL. This was a short-term, dose-intensive regimen centered on fractionated high-dose cyclophosphamide to maximize exposure and minimize time for repair of DNA damage among rapidly proliferating B cells; this alternated in tandem with a non-cross-resistant combination including high doses of MTX and ara-C (total therapy B program). The CR rate was 93%, and the 4 year event-free survival rate was 79% for patients with Burkitt lymphoma and 65% for patients with mature B-cell ALL. Only 4 of 133 children treated had HIV disease; all 4 achieved CR and 2 remain alive and in CR at the time of writing.26 Kantarjian et al. modified this regimen for use in adult ALL, reporting a CR rate of 91% and 5 year survival rate of 39%. Twenty-six HIV-negative patients with mature B-cell (Burkitt type) ALL were treated with this regimen as reported by Thomas et al. Twenty-one patients (81%) achieved a CR with a continuous CR rate at 3 years of 61%. The 3 year survival rate was 49% (77% for those younger than 60 years). The results reported here using the same regimen for patients with HIV infection compare favorably with those results, with a CR rate of 92%, a 2 year continuous CR rate of 52%, and a survival rate of 48%.

To our knowledge, few studies have specifically investigated AIDS-associated Burkitt leukemia and/or lymphoma, although these patients are frequently included in studies of AIDS-associated non-Hodgkin lymphoma. Treatment with CHOP has resulted in a CR rate of 30-50%, with a median survival of 6-9 months. A combination of cyclophosphamide, doxorubicin, and etoposide resulted in a CR rate of 57% with a median survival of 18 months among patients with various histologies of non-Hodgkin lymphoma. Using a rotational combination chemotherapy, Lopez et al. reported a CR rate of 83% and 5 year survival of 36% among 12 patients with HIV and Burkitt lymphoma. Since some patients have a poor outcome with more intensive regimens, a less intensive approach has been proposed. Using a low-dose M-BACOD regimen, a CR rate of 53% was reported among 17 patients with Burkitt lymphoma, and only 1 of the 9 patients achieving CR relapsed. In a randomized trial comparing low-dose versus standard-dose M-BACOD, 192 patients with various histologies of non-Hodgkin lymphoma were treated, including 35 with Burkitt lymphoma. The CR rates were not significantly different between low-dose patients (41%) and standard-dose patients (52%). Although the toxicity rate was lower in the low-dose group, there were no differences in overall or disease-free survival. The median survival for patients with Burkitt lymphoma was 41 weeks. Gisselbrecht et al. treated 141 patients (59 with small noncleaved cell lymphoma) with good performance status and no active opportunistic infection with doxorubicin, cyclophosphamide, vindesine, and bleomycin. Among patients with Burkitt lymphoma, the CR rate was 67%, and 40% of patients were alive at 2 years. The results reported here compare favorably with these studies. Using a dose-intensive regimen, the CR rate was 92%, with a projected disease-free survival rate of 52% at 2 years.

Patients with HIV-associated non-Hodgkin lymphomas have a twofold increased risk of developing opportunistic infections. In the current study, infectious complications occurred after 34% of the cycles. Eleven of the 13 patients (85%) experienced at least one infectious complication during the course of therapy. Usually this was a fever of unknown origin, although seven episodes of pneumonia were documented (two of suspected or documented fungal etiology). This dose-intensive regimen was universally myelosuppressive. Using the same regimen for the treatment of 26 patients with non-HIV Burkitt type...
adult ALL, 86% of 37 assessable courses were complicated by neutropenic febrile episodes.\textsuperscript{14} Therefore, the frequency of infectious complications in the current study is within the expected rate with this regimen and does not seem to be affected by the HIV status.

The most important finding in the current study is the potential benefit of HAART given during chemotherapy. Six of 7 patients who received HAART throughout their chemotherapy (i.e., started prior to or at the start of induction chemotherapy) remained alive and in CR after a median of 29 months (range, 7–45 months). One of 2 patients who started HAART late in the course of the chemotherapy remained alive and in CR after 33 months. All four patients who did not receive HAART died (three had performance status 4 at the start of therapy). Clearance of cyclophosphamide has been reported to be altered by the concurrent administration of antiretroviral agents,\textsuperscript{39} and the toxicity with chemotherapy was increased by antiretrovirals in some studies\textsuperscript{36} but not in others.\textsuperscript{35} In the current study, the administration of HAART was not associated with any identifiable increase in toxicity compared with that seen in non-HIV patients with ALL or Burkitt treated with the same regimen.\textsuperscript{14,20} Our results were particularly favorable considering that among the 9 patients treated with HAART, 7 had ALL or Stage IV disease, only 2 of 7 had pre-treatment CD4 counts $> 100/\mu L$ (only one $> 200/mm^3$), and 6 were older than 35 years of age. In addition, seven of the patients included had ALL-L3, and one additional patient with Burkitt lymphoma had bone marrow involvement. Overall, patients with ALL-L3 have a worse prognosis than those with Burkitt lymphoma,\textsuperscript{26,37} and in HIV-associated lymphomas bone marrow involvement is a feature of poor prognosis, with CR rates of 20 to 30%.\textsuperscript{30,33,38} In a recent multivariate analysis of prognostic factors in the treatment of HIV-associated non-Hodgkin’s lymphoma, 4 variables were independently associated with shorter survival: age $> 35$ years, Stage III or IV disease, CD4 count $< 100/\mu L$, and intravenous drug use (IVDU) as a risk factor for HIV.\textsuperscript{39} Small noncleaved cell (Burkitt-type) histology, together with CD4 count and IVDU, were adverse factors for CR duration.\textsuperscript{39} Since most adverse prognostic factors in this and other analyses\textsuperscript{33,40,41} are AIDS-related, the outcome of patients may be improved with enhanced immune recovery from the use of HAART. Most studies reported to date have either used no agents or single agent anti-viral therapy or started after chemotherapy was completed.\textsuperscript{31,32,42} Seven of the nine patients treated with HAART in the current series had at least two adverse prognostic factors (the CD4 count was not known in two patients, and the HIV risk factor was not known in another two patients) as defined by Straus et al.\textsuperscript{39} Thus, although the current series is small, the favorable results in this subgroup of patients (i.e., patients who received HAART with hyper-CVAD; 78% alive and in CR with a median follow-up of more than 2 years) suggest that this strategy is effective.

We conclude that hyper-CVAD is a highly effective regimen for the treatment of HIV-associated Burkitt lymphoma/leukemia. The use of HAART concomitant with the chemotherapy is feasible and may be associated with a favorable outcome. Thus, the availability of effective chemotherapy and anti-retroviral therapy opens the possibility of a prolonged disease-free survival for patients with two diseases previously considered invariably fatal.

REFERENCES


