Infusional Cyclophosphamide, Doxorubicin, and Etoposide in Human Immunodeficiency Virus– and Human T-Cell Leukemia Virus Type I–Related Non-Hodgkin’s Lymphoma: A Highly Active Regimen

By Joseph A. Sparano, Peter H. Wiernik, Margery Strack, Andrea Leaf, Norwin Becker, and Edward S. Valentine

Fourteen patients with poor-prognosis intermediate- to high-grade non-Hodgkin’s lymphoma (NHL) associated with human immunodeficiency virus (HIV) infection (12 patients) or human T-cell leukemia virus type I (HTLV-I) infection (two patients) received cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and etoposide 240 mg/m² administered as a continuous intravenous (IV) infusion over 4 days (infusional CDE); treatment was repeated every 28 or more days for up to six cycles. All HIV-positive patients had at least one poor prognostic feature, which included either extranodal disease (10 patients), Karnofsky performance status less than 70% (six patients), a CD4 count less than 100/µL (six patients), or a prior history of acquired immunodeficiency syndrome (AIDS; one patient). Both HTLV-I–positive patients had an elevated serum lactate dehydrogenase (LDH) level, a poor prognostic feature in that setting. Complete response (CR) occurred in 10 patients (71%; 95% confidence interval, 48% to 95%) and partial response (PR) occurred in three patients (21%), yielding an overall objective response rate of approximately 93%. The estimated Kaplan-Meier median survival was 17.4 months; seven of 12 HIV-positive patients are alive and disease-free with a median follow-up of 15 months (range, 7 to 24 months). Hospitalization was required after 19% of treatment cycles due to fever associated with granulocytopenia. Documented or suspected opportunistic infection occurred in five patients (36%), bacteremia occurred in three patients (21%), and candidemia occurred in one patient (7%). There was one treatment-related death attributable to disseminated aspergillosis. This pilot study suggests that infusional CDE may be a highly active regimen capable of producing durable remissions in a high proportion of patients with HIV-related NHL. Further study is required to confirm this observation. © 1993 by The American Society of Hematology.

Non-Hodgkin’s lymphoma (NHL) occurring in patients infected with the human immunodeficiency virus (HIV)1 or the human T-cell leukemia virus type I (HTLV-I)2,3 is increasing in incidence and is associated with a poor prognosis. Levine reviewed nine published trials describing at least 11 different chemotherapy regimens used in the treatment of HIV-related NHL; most patients received cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin; Eli Lilly, Indianapolis, IN), and prednisone (CHOP) or other regimens containing these drugs plus additional cytotoxic agents.1 The complete response (CR) rate ranged from 8% to 72% (median, 33%), median survival ranged from 2.6 to 15 months (median, 6 months), and opportunistic infection (OI) occurred in 20% to 78% (median, 28%).1 The poor response rate and survival for patients with HIV-related NHL is explained by their propensity to present with high-grade lymphoma and extranodal disease, to exhibit poor hematologic tolerance to chemotherapy, and to frequently experience fatal or treatment-limiting OI.1 Patients with NHL complicating HTLV-I infection also have a poor prognosis with conventional therapy; Shimoyama et al observed a 40% CR rate and a median survival of 8 months,2 and Gibbs et al observed a median survival of 6.5 months.3 Median survival was significantly worse for patients with an elevated serum lactate dehydrogenase (LDH) level.3

Some preclinical evidence suggests a therapeutic advantage for the administration of cytotoxic agents via an infusional schedule compared with a bolus schedule.4 Clinical evidence suggesting the importance of drug schedule includes (1) the observation of complete remissions after infusional cyclophosphamide therapy in patients with acute lymphocytic leukemia unlikely to respond to intravenous (IV) bolus cyclophosphamide,3 (2) the responses to IV infusional doxorubicin and vincristine (plus oral dexamethasone) in patients with multiple myeloma refractory to bolus doxorubicin,5 and (3) the significantly higher response observed in patients with small-cell lung cancer when IV etoposide is administered for 5 days (89%) compared with the same dose of etoposide given for 1 day (10%).6 Based on these observations, we hypothesized that patients with lymphoid tumors resistant to standard IV bolus chemotherapy might respond to the same drugs if administered as a continuous IV infusion. Hence, we treated 31 patients with relapsed or resistant intermediate- to high-grade NHL with cyclophosphamide, doxorubicin, and etoposide administered as a continuous IV infusion over 4 days (infusional CDE); the CR rate was 26% and the overall response rate was 45%.8 Furthermore, one HIV-positive patient and two HTLV-I–positive patients with relapsed or resistant NHL achieved CR with infusional CDE, with two patients remaining alive and disease-free at 38 months and 25 months; the third patient relapsed and died at 11 months. Based on these preclinical and clinical observations, we initiated a pilot study of infusional CDE as initial therapy for patients with HIV- or HTLV-I–related NHL.

MATERIALS AND METHODS

Patient selection. Patients were required to have Ann Arbor stage II to IV, biopsy- or cytology-proven diffuse large-cell, immunoblastic, or small noncleaved cell NHL and to be HIV- or HTLV-I-seropositive. OIs were controlled with appropriate therapy before the initiation of CDE. Patients with cytopenias or renal or hepatic dysfunction
were eligible, but the treatment was modified according to criteria described below. All pathologic and cytologic material was reviewed by a single hematopathologist (N.B.) and was classified according to the Working Formulation.9 The protocol was approved by the Institutional Review Board at Montefiore Medical Center, and informed consent was obtained from all patients.

Treatment. Patients received cyclophosphamide 187.5 mg/m²/d, doxorubicin 12.5 mg/m²/d, and etoposide 60 mg/m²/d as a continuous IV infusion for 4 days, with cycles repeated every 28 or more days for up to six cycles. The cumulative doses of cyclophosphamide, doxorubicin, and etoposide given with each cycle were 750 mg/m², 50 mg/m², and 240 mg/m², respectively. Cyclophosphamide and doxorubicin were admixed in 1 L of IV fluid and infused via a central venous catheter, while etoposide was dissolved in a separate L of IV fluid and administered via either a central venous catheter or a peripheral vein. Complete blood cell counts were obtained at least once weekly when possible or more frequently if indicated. The dose of CDE was reduced 25% from the initial dose in second or subsequent cycles if the nadir granulocyte count was less than 500/μL if the nadir platelet count was less than 25,000/μL, or if grade 3 or greater mucositis occurred; if severe granulocytopenia, thrombocytopenia, or mucositis recurred in subsequent cycles, CDE was reduced by 50% of the initial dose. Granulocyte-colony stimulating factor (G-CSF; 5 μg/kg) was administered subcutaneously or IV beginning 4 hours after the completion of the infusion at the discretion of the treating physician in patients who experienced severe granulocytopenia. Patients with abnormal baseline organ function were not excluded; three patients with a granulocyte count of less than 1,000/μL received a 25% to 50% dose reduction in cycle 1, and one patient with a total bilirubin of 11.4 mg/dL (hepatitis B surface antigen-positive and lymphomatous infiltration of the liver) had the dose of doxorubicin reduced 75% during cycle 1. All patients received Pneumocystis carinii pneumonia (PCP) prophylaxis (160 mg trimethoprim/800 mg sulfamethoxazole once or twice daily), allopurinol 300 mg orally daily, and IV hydration. No antiretroviral therapy was given during the period of chemotherapy administration, but patients who completed CDE with a CD4 count less than 400/μL received zidovudine 15 mg five times daily. Patients who developed an OI had CDE withheld until the infection was controlled with appropriate therapy; if a patient with OI was in CR or if three or more cycles of CDE had been given, further CDE was withheld.

CNS prophylaxis and treatment. Patients with small noncleaved cell lymphoma or bone marrow involvement received CNS prophylaxis consisting of methotrexate (MTX) 15 mg administered intrathecally on days 1 and 4 of each cycle and whole brain radiation therapy (WBRT). Leucovorin 15 mg was administered orally every 6 hours for eight doses beginning 12 hours after each intrathecal injection of MTX. WBRT began with the second or third cycle of CDE in responding patients, and consisted of 24 Gy in 12 fractions (five fractions weekly, 2 Gy per fraction) using a German Helmet field via right and left lateral portals. Patients with lymphomatous meningitis also received intrathecal MTX and WBRT. However, MTX was administered via lumbar puncture or Ommaya reservoir three times weekly until the cytology was negative on two consecutive occasions, then twice weekly for 2 weeks, then weekly for 4 weeks, then monthly for up to 1 year after the diagnosis of lymphomatous meningitis was made. In addition, WBRT was implemented immediately in patients with lymphomatous meningitis, rather than waiting for evidence of systemic response.

Evaluation of disease activity. All patients underwent staging evaluation, which included physical examination, chest x-ray, computerized tomography of the abdomen, pelvis, brain, or sites of known disease activity, bone marrow aspiration and biopsy, lumbar puncture with cytologic analysis of the cerebrospinal fluid (CSF), and a CD4 lymphocyte count. Standard criteria were used to define response. Response evaluation of all known sites of disease was performed after every two cycles of therapy, at the completion of therapy, and every 3 to 6 months thereafter. CR was defined as disappearance of all evidence of malignant disease. Partial response (PR) was defined as a greater than 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions.

Statistical analysis. Survival was estimated using the product-limit method of Kaplan and Meier.10 Survival was calculated from the time at which patients began treatment with infusional CDE.

RESULTS

Patient characteristics. The characteristics of the study population are summarized in Table 1, and the characteristics and outcome for each individual patient are shown in Table 2. Twelve patients were HIV-positive and two were HTLV-I-positive. All HIV-positive patients had at least one poor prognostic feature as described by Kaplan et al,11 which included either extranodal disease (10 patients), Karnofsky performance status less than 70% (six patients), a CD4 count less than 100/μL (six patients), or a history of prior acquired immunodeficiency syndrome (AIDS; one patient). Likewise, both HTLV-I-positive patients had an elevated serum LDH level (1,545 and 729 IU/L; Table 2), a factor associated with a poor prognosis in that setting.12 Extranodal sites of involvement in the HIV-positive patients included the bone marrow (three patients), lung (two patients), gastrointestinal tract (two patients), skin (three patients), and the liver, sinuses, bone, and placenta in one patient each. One HTLV-I-positive patient had pleural involvement, and both had phenotypic

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Gender (male/female)</th>
<th>Median age (range)</th>
<th>HIV-HTLV-I-positive</th>
<th>HIV risk factors</th>
<th>Poor prognostic features</th>
<th>Prior AIDS</th>
<th>CD4 count &lt;100/μL</th>
<th>Karnofsky performance status &lt;70%</th>
<th>Extranodal disease</th>
<th>Elevated serum LDH</th>
<th>Bulky disease &gt;7 cm</th>
<th>Stage</th>
<th>Histology</th>
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<tbody>
<tr>
<td>14</td>
<td>10/4</td>
<td>39 years (30-63)</td>
<td>12/2</td>
<td>Homosexual</td>
<td>2</td>
<td>1</td>
<td>6* (median, 87/μL; range, 2 to 484)</td>
<td>7 [8]* (median, 60%; range, 20% to 100%)</td>
<td>11 [10]*</td>
<td>11 [9]* (median, 383 IU/L; range, 142 to 1,820)</td>
<td>7 [6]*</td>
<td>II/III</td>
<td>Diffuse large cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intra venous drug user</td>
<td>8</td>
<td></td>
<td></td>
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<td></td>
<td>Heterosexual</td>
<td>2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CD4 count available in 11 HIV-positive patients.
† Numbers in brackets indicate number of HIV-positive patients with that feature.
‡ LDH ≥250 IU/L.
markers consistent with T-cell derivation, but neither patient had hypercalcemia or lytic bone lesions. Six patients (43%) had OI that occurred before (four patients) or concomitantly with (two patients) the diagnosis of AIDS before the development of NHL. The types of OI in the patient with AIDS included PCP and disseminated cryptococcosis; another patient had esophageal candidiasis, which occurred concomitantly with, but not before the diagnosis of NHL. Other OIs preceding NHL in patients not considered to have AIDS included cutaneous Mycobacterium marinum, oral candidiasis, and herpes zoster in one patient each; one other patient had pneumonitis of unknown etiology that was not documented to be PCP.

**Treatment outcome.** CR occurred in 10 patients (71%; 95% confidence interval, 48% to 95%) and PR occurred in three patients (21%), yielding an overall response rate of approximately 93% (Table 2). The estimated Kaplan-Meier median survival for the entire treatment group (and for the HIV-positive patients only) was 17.4 months (Fig 1). Seven of 12 HIV-positive patients are alive and disease-free with a median follow-up of 15 months (range, 7 to 24). The mean and median number of cycles given to responding patients were 4.8 and five cycles, respectively (range, three to six cycles). While the numbers of patients who were HIV-positive and HTLV-I-positive were too small for comparison, CRs occurred in both groups. Eight of 12 HIV-positive patients (67%) achieved a CR, while both HTLV-I-positive patients achieved a CR. One patient, who presented with a 20-× 15-cm axillary mass, received local irradiation to the axilla after achieving a CR; no other patient received radiation therapy, except for those receiving CNS treatment or prophylaxis.

### Table 2. Study Population and Outcome

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>RF</th>
<th>PS</th>
<th>Prior OI</th>
<th>CD4</th>
<th>His</th>
<th>Stage</th>
<th>EN Site</th>
<th>LDH</th>
<th>Response</th>
<th>Survival (mo)</th>
<th>Death</th>
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<tr>
<td>30/M</td>
<td>HS</td>
<td>80</td>
<td>—</td>
<td>58</td>
<td>J</td>
<td>II*</td>
<td>—</td>
<td>142</td>
<td>CR</td>
<td>24+</td>
<td>—</td>
</tr>
<tr>
<td>35/F</td>
<td>No</td>
<td>70</td>
<td>+ (1)</td>
<td>NA</td>
<td>H</td>
<td>IV*</td>
<td>Placenta, lung</td>
<td>287</td>
<td>PR</td>
<td>18</td>
<td>L</td>
</tr>
<tr>
<td>40/M</td>
<td>IV</td>
<td>80</td>
<td>+ (2)</td>
<td>2</td>
<td>H</td>
<td>IV</td>
<td>Lung</td>
<td>628</td>
<td>PR</td>
<td>16+</td>
<td>—</td>
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<tr>
<td>32/M</td>
<td>IV</td>
<td>80</td>
<td>—</td>
<td>87</td>
<td>G</td>
<td>III</td>
<td>Lung</td>
<td>140</td>
<td>CR</td>
<td>15+</td>
<td>—</td>
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<tr>
<td>45/M</td>
<td>IV</td>
<td>60</td>
<td>—</td>
<td>165</td>
<td>J</td>
<td>IV*</td>
<td>Liver</td>
<td>306</td>
<td>CR</td>
<td>15+</td>
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<tr>
<td>39/M</td>
<td>HS</td>
<td>30</td>
<td>—</td>
<td>240</td>
<td>J</td>
<td>II</td>
<td>—</td>
<td>387</td>
<td>CR</td>
<td>12+</td>
<td>—</td>
</tr>
<tr>
<td>32/M</td>
<td>HS</td>
<td>80</td>
<td>—</td>
<td>114</td>
<td>G</td>
<td>IV*</td>
<td>Skin</td>
<td>477</td>
<td>CR</td>
<td>11</td>
<td>L</td>
</tr>
<tr>
<td>63/F†</td>
<td>—</td>
<td>20</td>
<td>—</td>
<td>H</td>
<td>IV*</td>
<td>Sinus, bone</td>
<td>383</td>
<td>CR</td>
<td>7+</td>
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<tr>
<td>40/M</td>
<td>IV</td>
<td>60</td>
<td>++</td>
<td>17</td>
<td>H</td>
<td>III</td>
<td>—</td>
<td>729</td>
<td>CR</td>
<td>6+</td>
<td>—</td>
</tr>
<tr>
<td>37/F†</td>
<td>—</td>
<td>100</td>
<td>—</td>
<td>G</td>
<td>IV*</td>
<td>—</td>
<td>—</td>
<td>1545</td>
<td>CR</td>
<td>10+</td>
<td>—</td>
</tr>
<tr>
<td>38/M</td>
<td>IV</td>
<td>80</td>
<td>+ (3)</td>
<td>418</td>
<td>J</td>
<td>IV*</td>
<td>Marrow, cecum</td>
<td>1820</td>
<td>CR</td>
<td>5</td>
<td>L</td>
</tr>
<tr>
<td>39/M</td>
<td>IV</td>
<td>60</td>
<td>+ (4)</td>
<td>119</td>
<td>J</td>
<td>IV*</td>
<td>Marrow, stomach</td>
<td>300</td>
<td>CR</td>
<td>4</td>
<td>L</td>
</tr>
<tr>
<td>45/M</td>
<td>IV</td>
<td>60</td>
<td>+ (5)</td>
<td>49</td>
<td>H</td>
<td>IV</td>
<td>Skin</td>
<td>225</td>
<td>PR</td>
<td>4</td>
<td>I</td>
</tr>
<tr>
<td>43/F</td>
<td>IV</td>
<td>30</td>
<td>—</td>
<td>11</td>
<td>G</td>
<td>IV</td>
<td>Marrow</td>
<td>1450</td>
<td>PD</td>
<td>1.5</td>
<td>L</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; RF, risk factor for HIV infection; HS, homosexual; IV, intravenous drug abuse; No, none acknowledged; OI, opportunistic infection; PS, Kaposi's sarcoma; CD4, CD4+ cell count; HIV, human immunodeficiency virus; NHL, non-Hodgkin's lymphoma; CR, complete response; PR, partial response; PD, progressive disease; NE, not evaluable; L, lymphoma; I, infection (aspergillosis).

† Denotes bulky disease >7 cm in diameter.

‡ Prior OI (opportunistic infection): +, presence of OI before or concomitant with the diagnosis of lymphoma: (1) pneumonitis of undetermined etiology (before), (2) cutaneous Mycobacterium marinum (concomitant), (3) thrush (before) (4) candida esophagitis (concomitant), (5) herpes zoster (before); ++, denotes OI that occurred before lymphoma and which met the criteria for the diagnosis of AIDS (PCP and cryptococcosis).
free at 17 months; this patient developed pneumonitis of unknown etiology 1 week after completing the third cycle of infusional CDE, which obscured evaluating the biopsy-proven lymphomatous lung nodules, his only site of disease. He improved clinically with empiric antibiotic therapy, but the pulmonary infiltrates resolved gradually over 12 months, eventually showing no evidence of residual nodular densities, most likely indicating that he may in fact have had a CR.

Six patients (43%) have died after a median follow-up of 11.5 months; five have died of progressive lymphoma, and one has died of infection (disseminated aspergillosis) (Table 2). Three of 10 patients who achieved a CR have relapsed and died of progressive lymphoma.

CNS progression or relapse. Based on the treatment protocol guidelines, six patients should have received prophylactic CNS therapy. In two responding patients with small noncleaved lymphoma and an initial normal bone marrow and CSF examination, lymphomatous meningitis developed after the second cycle of chemotherapy, but before the initiation of prophylactic WBRT, despite intrathecal MTX administered on the first and fourth day of each treatment cycle. Lymphoma cells were eradicated from the CSF in both patients after treatment with WBRT plus more frequent administration of intrathecal MTX, and they continue to be alive and disease-free 24 months and 12 months after their initial diagnosis. One patient with diffuse, small noncleaved cell lymphoma and lymphomatous hepatic involvement had a complete remission, but did not receive prophylactic CNS therapy because the histology was initially interpreted to be a large-cell lymphoma; despite the absence of prophylactic CNS therapy, the patient is alive and disease-free without evidence of systemic or CNS lymphoma. Of interest, this patient developed a Bell’s palsy after the completion of therapy; examination of the CSF showed no malignant cells, and the palsy resolved spontaneously without irradiation or intrathecal chemotherapy. Finally, three other patients who had either diffuse, small-cell noncleaved histology (n = 2) and/or lymphomatous bone marrow involvement (n = 3) received prophylactic CNS therapy, but died of systemic disease progression.

Toxicity and infectious complications. Sixty-four treatment cycles were administered. Twelve cycles (19%) were complicated by fever associated with granulocytopenia requiring hospitalization and parenteral antibiotics. At least one nadir blood count was obtained for 49 treatment cycles; severe granulocytopenia (≤500/μL) and thrombocytopenia (≤20,000/μL) occurred in 23 cycles (47%) and 10 cycles (20%), respectively. The dose of infusional CDE was reduced in 28 treatment cycles (44%). G-CSF was used at the discretion of the treating physician in 17 treatment cycles (27%). G-CSF was used most often in patients who presented with fever and granulocytopenia or prophylactically in conjunction with a reduced dose of infusional CDE in patients who had previously experienced severe granulocytopenia, making it difficult to determine the effect of G-CSF in ameliorating CDE-related granulocytopenia. One patient developed hematochezia unassociated with thrombocytopenia during cycle 1, which resolved and was most likely tumor-related. Mucositis occurred in two patients, one of whom also had severe candida esophagitis. All patients developed alopecia. Nausea was generally mild and controlled with prochlorperazine. No patients developed tumor lysis syndrome.

Nine infections occurred in six patients. Five infections were considered opportunistic, one of which was lethal. The lethal infection was disseminated aspergillosis, which occurred after cycle 4 of infusional CDE. Another patient (HTLV-I-positive) developed cryptococcal meningitis after cycle 2 of CDE and was treated with amphotericin-B followed by fluconazole; she received four additional cycles of CDE without recurrence of the infection. Other OIs included one episode each of candida esophagitis, herpes labialis, and pneumonitis of unknown etiology that improved with empiric antimicrobial therapy. Other nonopportunistic infectious complications included bacteremia in two patients (coagulase-negative staphylococci [n = 1], enterococcus [n = 1]), candidemia associated with a central venous catheter (n = 1), and hepatitis C infection (n = 1). One patient with coagulase-negative staphylococcal bacteremia associated with a Hickman catheter had a pneumonic infiltrate consistent with septic embolization treated with parenteral antibiotics and catheter removal. All infections resolved with appropriate therapy, with the exception of the patient with disseminated aspergillosis, in whom the diagnosis was made on postmortem examination. Two patients were known to have hepatitis B (n = 1) or hepatitis C (n = 1) infection before the initiation of therapy, and both are alive and progression-free at 15 and 16 months, respectively.

DISCUSSION

We observed a 71% CR rate in 14 patients with HIV- or HTLV-I-related NHL treated with infusional CDE; the estimated Kaplan-Meier median survival was 17.4 months. If only HIV-positive patients are considered, the results are equally impressive, with a 67% CR rate and equivalent median survival. These results appear promising when compared with the outcome of previously published trials involving patients with HIV,1 or HTLV-I-related2 NHL.

We deliberately selected patients with poor prognostic features for this pilot trial, since we wanted to assure that a beneficial outcome, if observed, could not be attributed to selection bias. Kaplan et al noted a poorer survival for patients with extranodal involvement, a Karnofsky performance status (KPS) of less than 70%, a CD4 count of less than 100/μL, or a prior history of AIDS; the median survival for each of these groups was 4.2 (±1.3) months, 3.8 (±1.1) months, 4.1 (±1.0) months, and 2.2 (±0.77) months, respectively.11 Likewise, Levine et al found Karnofsky performance status less than 70%, a prior AIDS diagnosis, or bone marrow involvement to be associated with a poor prognosis.12 Every HIV-positive patient in our study had at least one of the poor prognostic features defined by Kaplan et al.11 In addition, both HTLV-I-positive patients had an elevated serum LDH level, a factor associated with an adverse prognosis in that setting.2 Therefore, we feel that we succeeded in treating a group of patients expected to have a poor prognosis, and that the encouraging result observed in our pilot study is not attributable to selecting a favorable patient population. However, such analyses of prognostic factors must be interpreted cautiously and may
not be applicable to patients selected to receive chemotherapy. For example, 19 of the 84 patients reported by Kaplan et al11 who were studied to identify prognostic features never received chemotherapy. In that series, 13 of 65 patients (20%) treated with chemotherapy had a prior AIDS diagnosis, compared with 14 of 19 patients (74%) not treated with chemotherapy, illustrating that only more favorable patients were selected to receive combination chemotherapy. Therefore, the results of therapeutic trials, including our own, may not be applicable to all patients with HIV-related NHL, since the decision to treat such a patient represents an element of selection. In order for prognostic features to be more meaningful in this setting, they should be analyzed in a group of patients who are selected to receive chemotherapy and who receive a uniform treatment regimen. Hence, when the characteristics of our study group are compared with the characteristics of patients in four other trials that included a uniform treatment protocol,11,13-15 it is again evident that our encouraging results cannot be explained on the basis of favorable patient selection (Table 3). In fact, patients in our study group tended to have lower CD4 counts and to have a poorer performance status, features associated with an adverse prognosis. Furthermore, Levine et al15 have confirmed that in 42 patients with HIV-related NHL selected to receive low-dose m-BACOD plus intrathecal cytarabine, the presence of a low CD4 count (<200/μL), prior AIDS diagnosis, bone marrow involvement, and stage IV disease were all associated with poor survival, indicating that these features have prognostic value even in patients selected to receive chemotherapy.

The feature that distinguishes our study is not only the high CR rate, but, more importantly, the apparently improved median survival. Since patients with HIV-related NHL may die of overwhelming OI or an HIV-related wasting syndrome, as well as progressive lymphoma, it is possible that improved supportive care and/or antiretroviral therapy may also have contributed to improved survival. However, antiretroviral therapy was discontinued during the period of chemotherapy administration in our study, and prophylactic therapy consisted only of trimethoprim-sulfamethoxazole, measures that are comparable to those used by other groups. Furthermore, while OIs and other manifestations of progressive AIDS are frequent causes of death in such patients, most patients still die of progressive lymphoma. Of the 42 patients treated with low-dose m-BACOD plus intrathecal cytarabine by Levine et al,15 21 (50%) died of progressive lymphoma, nine (21%) died of AIDS-related complications, three (7%) died of unknown causes, one (2%) died of bacterial sepsis, and one (2%) committed suicide. Improved supportive care and antiviral therapy is unlikely to prolong the life of a patient with a clinically aggressive lymphoma involving extranodal sites that is refractory to treatment. Therefore, we feel that the improved survival observed in our study is attributable to treatment with a more effective antilymphoma regimen, rather than the expertise of our group in supporting HIV-infected patients.

Two patients in our series had HTLV-I-related NHL. We elected to include these patients in our pilot study since the prognosis for these patients is also poor with standard chemotherapy, and since the course of their illness may also be complicated by OIs.2,3 While no conclusions can be made regarding the efficacy of infusional CDE in these patients, our encouraging results in HIV-related NHL suggest that continued study is warranted in patients with HTLV-I-related NHL as well.

No patient in our study died of an isolated CNS relapse. Only patients with diffuse, small noncleaved lymphoma or lymphomatous marrow involvement received prophylactic CNS therapy. Therefore, our findings suggest that restricting CNS prophylaxis to those specific groups may be a reasonable strategy. However, the development of lymphomatous meningitis in two patients despite prophylactic intrathecal MTX suggests the schedule used may not be effective in preventing CNS relapse; alternative options could include more frequent intrathecal MTX administration, alternation with or substitution by cytarabine, administration of systemic high-dose MTX, or perhaps earlier implementation of prophylactic WBRT. Fortunately, both patients with isolated CNS relapse

### Table 3. Clinical Trials of Chemotherapy Regimens in AIDS-Related Non-Hodgkin's Lymphoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>CD4 Count (cells/μL)</th>
<th>Prior AIDS</th>
<th>KPS</th>
<th>Extranodal Disease</th>
<th>Bone Marrow--Positive</th>
<th>CR%</th>
<th>Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>m-BACOD13</td>
<td>13</td>
<td>368*</td>
<td>NR</td>
<td>70*</td>
<td>11 (86%)</td>
<td>2 (15%)</td>
<td>7 (64%)</td>
<td>11.0</td>
</tr>
<tr>
<td>COMET-A11</td>
<td>38</td>
<td>1641*</td>
<td>8 (21%)</td>
<td>751</td>
<td>25 (68%)</td>
<td>NR</td>
<td>19 (50%)</td>
<td>6.0</td>
</tr>
<tr>
<td>CHOP14</td>
<td>30</td>
<td>200-290†</td>
<td>4 (13%)</td>
<td>841</td>
<td>21 (70%)</td>
<td>7 (23%)</td>
<td>16 (53%)</td>
<td>8.0-11.4</td>
</tr>
<tr>
<td>Low-dose m-BACOD15</td>
<td>42/35†</td>
<td>150†</td>
<td>81 (23%)</td>
<td>≥80%*</td>
<td>23* (66%)</td>
<td>61 (17%)</td>
<td>16 (38%)</td>
<td>5.6</td>
</tr>
<tr>
<td>Infusional CDE (current study)</td>
<td>12</td>
<td>87* (1071)</td>
<td>1 (8%)</td>
<td>60* (641)</td>
<td>10 (83%)</td>
<td>3 (25%)</td>
<td>8 (67%)</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Abbreviations: KPS, Karnofsky performance status; NR, not reported; m-BACOD, methotrexate, bleomycin, doxorubicin, vincristine, and dexamethasone; COMET-A, cyclophosphamide, vincristine, methotrexate, leucovorin, etoposide, and cytarabine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

* Median.
† Mean.
‡ Evaluable.
§ CR rate based on all patients treated.
† CD4 count available for 33 patients.
† CD4 count available for 30 patients.
appear to have been cured. While further study will be required to determine the optimal CNS prophylactic regimen, our study suggests that not all patients may require such prophylaxis.

The incidence of OI was comparable in this trial when compared with other trials of HIV-related NHL. Other serious toxicities occurred frequently, as expected. One patient died of disseminated aspergillosis, an infection that typically occurs in patients with prolonged chemotherapy-induced granulocytopenia, but that was also recently described in HIV-positive patients lacking granulocytopenia. Toxicity was manageable with appropriate dose reduction and with the use of standard supportive care procedures now routinely used for patients with fever associated with severe granulocytopenia (ie, inpatient parenteral antibiotic therapy). No patients died of bacterial sepsis or hemorrhage, and no patient developed tumor lysis syndrome.

Hematopoietic growth factors were used at the discretion of the treating physician, since they became commercially available during the course of this study. However, we were not able to draw any conclusions regarding the ability of G-CSF to ameliorate granulocytopenia in our study, since the dose of infusedional CDE was usually reduced when combined with G-CSF. We have recently found that granulocyte, macrophage-CSF (GM-CSF) reduces the incidence of severe granulocytopenia and febrile episodes complicating infusedional CDE in patients with non–HIV-related NHL (unpublished observation). Therefore, just as Kaplan et al have shown that GM-CSF reduces the severity and duration of granulocytopenia and the frequency of febrile granulocytopenia in patients with HIV-related NHL receiving CHOP, the prophylactic use of hematopoietic growth factors might also be expected to reduce the risk of severe granulocytopenia and fever in patients with HIV-related NHL receiving infusedional CDE. However, the combination of hematopoietic growth factors with infusedional CDE should proceed cautiously in carefully performed clinical trials. For example, GM-CSF significantly increases p24 antigen expression in patients with HIV-related NHL receiving CHOP, a finding not observed in comparable patients receiving CHOP without GM-CSF. The clinical consequences of this observation, if any, are currently unknown.

In conclusion, infusedional CDE appears to be an effective regimen capable of producing durable remissions in a high proportion of patients with HIV-related NHL who are expected to have a dismal prognosis with conventional chemotherapy. Further study is necessary to confirm this encouraging result, and to carefully study the virologic and clinical consequences of combining this regimen with hematopoietic growth factors.

REFERENCES


Infusional cyclophosphamide, doxorubicin, and etoposide in human immunodeficiency virus- and human T-cell leukemia virus type I-related non-Hodgkin’s lymphoma: a highly active regimen

JA Sparano, PH Wiernik, M Strack, A Leaf, N Becker and ES Valentine

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