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Oral Combination Chemotherapy in Conjunction With Filgrastim (G-CSF) in the Treatment of AIDS-Related Non-Hodgkin's Lymphoma: Evaluation of the Role of G-CSF; Quality-of-Life Analysis and Long-Term Follow-Up

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In 1993 we reported the efficacy and toxicity profile of an oral combination regimen administered to 18 patients with AIDS-related lymphoma (NHL-1 study). We observed a 61% response rate; 39% one-year survival rate; nearly two-thirds of patients developed ≥ grade 3 leukopenia; and 28% of cycles were associated with febrile neutropenia. These results prompted us to shorten the duration of therapy and to add G-CSF to ameliorate the myelosuppression. Twenty patients with biopsy-proven AIDS-related lymphoma were treated with three 6-week cycles of oral chemotherapy consisting of lomustine (CCNU) 100 mg/m^2 on day 1, cycles no. 1 and 3; etoposide 200 mg/m^2 days 1–3; cyclophosphamide and procarbazine both 100 mg/m^2 days 22–31; and G-CSF 5 μg/kg subcutaneously days 5–21 and days 33–42 (NHL-2 study). The following analyses were undertaken: (1) evaluation of toxicity and efficacy parameters for patients in the current (NHL-2) study; (2) analysis of the clinical role of G-CSF by (historical) comparison with the NHL-1 study of the same regimen without G-CSF; (3) quality-of-life assessments using the Functional Living Index—Cancer (FLIC) and Brief Symptom Inventory (BSI) instruments for all 38 patients (NHL-1+2); and (4) long-term follow-up for all 38 patients. In the current study the overall objective response using ECOG criteria was 70% (95% CI, 50–90%) with 6 CRs (30%) and 8 PRs (40%). The median survival duration was 7.3 months (range: 0.5–51$^+$

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months). One patient developed CNS relapse. There were no significant differences with respect to demographics or prognostic factors between the patient populations of the NHL-1 study and the current study ($P > 0.2$ for each factor).

Myelosuppression was the major toxicity in both studies. In the current study versus the NHL-1 study, although the lower incidences of grade 3/4 myelosuppression (51% vs. 64%) and febrile neutropenia (17% vs. 28%) on a per cycle basis were not statistically significant, fewer patients (40% vs. 60%) were affected. However, the severity of myelotoxicity was lessened with the addition of G-CSF, measured in terms of the discontinuation of therapy, myelotoxic deaths, and freedom from grade 3/4 myelotoxicity ($P < 0.02$). The number of hospitalizations for febrile neutropenia (7 in the NHL-2 study vs. 13 in the NHL-1 study) was also significantly different ($P < 0.05$). Quality-of-life analysis confirmed no significant functional or psychological deterioration during therapy except for patients experiencing febrile neutropenia, whose functional capacity deteriorated ($P < 0.04$). The 1-year, 18-month, and 2-year survival rates for the combined studies (38 patients) were 32%, 21%, and 13%, respectively. At time of death 49% of patients were free from progression of their lymphoma. Administration of the oral regimen has resulted in 13% of patients surviving two years, and half of patients surviving free from progression of their lymphoma. This regimen is efficacious and considerate of patient quality-of-life issues. The addition of G-CSF to the regimen decreases the frequency of hospitalization for febrile neutropenia. Am. J. Hematol. 66:178–188, 2001.

Key words: AIDS; non-Hodgkin's lymphoma; oral chemotherapy; quality of life

INTRODUCTION

In 1993 we reported the efficacy and toxicity profile of a novel oral combination regimen administered to 18 patients with AIDS-related non-Hodgkin's lymphoma (that study is referred to hereafter as the NHL-1 study) [1]. The rationale for the initial study was based on the following points [1]: all of the agents in the regimen [lomustine (CCNU), etoposide, cyclophosphamide, and procarbazine] are active in lymphoma when used as single agents, with response rates ranging between 10% and 40%. To varying degrees, these agents have been incorporated into front-line combination chemotherapy regimens for de novo non-Hodgkin's lymphoma. Combination chemotherapy is superior to single agents for this disease. Both CCNU and procarbazine cross the blood–brain barrier, a quality that may be of value given the proclivity for dissemination and relapse in this site in HIV-infected patients. Corticosteroids were omitted from the regimen because of additional immunosuppressive effects and possible promotion of tumor growth in patients with Kaposi's sarcoma. And finally, the regimen avoids the potential of cardiotoxicity seen with doxorubicin-based combination chemotherapy regimens.

In this current study (which is referred to herein as the NHL-2 study) we shortened the duration of treatment from five cycles of therapy to three cycles and added filgrastim [granulocyte colony-stimulating factor (G-CSF)], in the hope of lessening myelosuppression. G-CSF was chosen rather than GM-CSF, since the latter cytokine had been shown to up-regulate HIV viral expression [2–4]. We sought to evaluate toxicity and efficacy parameters of the current NHL-2 study versus the original NHL-1 study. In addition, we report long-term follow-up, a quality-of-life assessment, and an evaluation of prognostic factors for all 38 patients followed on both studies (NHL-1+2).

PATIENTS AND METHODS

Patient Selection Criteria

Patients with non-Hodgkin's lymphoma who met Centers for Disease Control (CDC) clinical criteria for AIDS were entered onto protocol between September 1992 and December 1995 [5]. A total of 20 patients were evaluated and followed as part of the current study. Follow-up for all 38 patients (NHL-1+2) is reported through October 1999, including 3 patients who were alive at the time of our original report [1]. Participating institutions included Albany Medical Center Hospital (17 patients), St. Clare's Hospital and Health Center [2], and Adirondack Medical Center [1]. Signed informed consent was obtained from all patients in keeping with FDA and institutional guidelines upon IRB approval. All patients had histologically confirmed non-Hodgkin's lymphoma clinicopathological stage I through IV according to Ann Arbor criteria with measurable or assessable disease [6]. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 3 [7] and life expectancy of at least 6 weeks were required. Before registration patients had to have a WBC count $\geq 1{,}500/\mu l$ platelet count $\geq 50{,}000/\mu l$, serum creatinine content ≤ 3.0 mg/dl, and serum bilirubin content ≤ 3.0 mg/dl. Patients with clinical, radiographic, or CSF cytologic evidence of CNS lymphoma were ineligible.

At enrollment all patients underwent complete history

TABLE I. Chemotherapy Regimen

Drug	Dose (mg/m^2)[a]	Day(s)
CCNU[b]	100	1
Etoposide	200	1–3
Cyclophosphamide	100	22–31
Procarbazine	100	22–31
Filgrastim (G-CSF)	5 μg/kg[c]	5–21; 33–42

[a]All drugs given orally.
[b]CCNU administered during cycles 1 and 3. A cycle is repeated every 6 weeks. [Patients were considered to have completed a half-cycle of therapy if days 1–3 of the regimen were administered.
[c]G-CSF administered as a daily subcutaneous injection; an initial G-CSF dose of 5 μg/kg is rounded to either 300 or 480 μg to facilitate patient administration.

TABLE II. Hematologic Dose Modifications*

WBC count (/ml)	Platelet (/ml)	%Drug dose[a]	G-CSF[b]
≥4,000	≥100,000	100%	5
3,000–3,999	≥100,000	100%	5
3,000–3,999	75–99,999	75%	5
1,500–2,999	50–74,999	50%	5
≤1,499	≤49,999	0%	5

*All dose modifications made on day of therapy (i.e., days 1 and 22 only). All patients received drug treatment provided the WBC count was ≥1,500/μl and platelet count ≥50,000/ml. Treatment was delayed until counts returned to those levels or until 3 weeks had elapsed, whichever occurred first. At that time, patients who did not meet these criteria were removed from study.
[a]Dose reduction was made for all chemotherapeutic drugs. For patients who required hospitalization for fever and neutropenia, the next cycle was administered upon recovery at 50% dose reduction from the preceding cycle provided this was attributable to cytotoxic chemotherapy; 25% dose escalation afterwards to return to 100% dose.
[b]G-CSF was administered at a dose of 5 μg/kg (with the total dose rounded to 300 or 480 μg to facilitate patient administration). During G-CSF administration, complete blood counts with differential were monitored twice weekly; if at any time during post nadir period (beyond days 15 and day 36) ANC ≥10,000/μl, G-CSF is discontinued.

and physical examination; blood counts, chemistry profiles and CD4 lymphocyte counts; and baseline quality-of-life assessments, including the Functional Living Index—Cancer (FLIC) and Brief Symptom Inventory (BSI). The administration and methodology for these two procedures respectively have been previously reported in detail [1]. Patients also had chest X ray; computed tomographic scans of the head, chest, abdomen, and pelvis; bone marrow aspiration and biopsy; and lumbar puncture for CSF cytology. During the course of the study, patients underwent the identical clinical evaluations as originally reported [1] with two exceptions. Complete blood cell counts with differential were performed on the day of starting chemotherapy and twice weekly during the period of G-CSF administration. Thorough evaluation of extent of disease was undertaken upon completion of the first cycle of therapy and at the conclusion of the third cycle of therapy.

Treatment Regimen

Patients received three six-week cycles of oral combination chemotherapy consisting of lomustine (CCNU) 100 mg/m^2 day 1, cycles no. 1 and 3; etoposide 200 mg/m^2 days 1–3; cyclophosphamide 100 mg/m^2days 22–31; and procarbazine 100 mg/m^2 days 22–31. G-CSF (Amgen, Inc., Thousand Oaks, CA) was administered as a subcutaneous injection at a dose of 5 μg/kg (rounded to either 300 or 480 μg total dose to facilitate administration) on days 5–21 and days 33–42 (see Table I). If the ANC count was ≥10,000/μl beyond the nadir period for each 3-week portion of the chemotherapy regimen, days no. 15 and 36, respectively, G-CSF was discontinued. Antiemetics were prescribed by the treating physician team, and no prehydration was required. All patients received prophylaxis for *Pneumocystis carinii* pneumonia (PCP), which was prescribed by the treating physician. Other prophylactic antibiotic regimens for opportunistic infection and concomitant antiretroviral therapy were at the discretion of the treating physician. Protease inhibitors were not available during the conduct of this study.

All dose modifications for hematologic toxicities were made on the basis of WBC and platelet counts determined on the days of treatment (days 1 and 22), as outlined in Table II. Dose modifications for hepatic and renal toxicity were prescribed as previously [1]. A 50% dose reduction in cyclophosphamide was made for hemorrhagic cystitis. If this recurred cyclophosphamide was discontinued.

All patients were to receive at least one full cycle (6 weeks) of therapy, which was considered induction. Patients were completely restaged after their first cycle and treated with two additional cycles of chemotherapy, at which point another restaging evaluation was performed. Patients with a complete or partial remission and stable disease were followed. All patients with progressive disease at any point were removed from study.

Pathology Review

The pathology slides of lymphoma were reviewed (by TN) in all 20 patients and were classified by the Working Formulation criteria [8] and Revised European-American Lymphoma (REAL) classification [9]. In 16 cases, paraffin blocks were obtained for immunoperoxidase studies. In six of these cases frozen tissue was also available for gene rearrangement studies: immunoglobulin heavy chain, light chain, and T-cell receptor β-chain gene rearrangements. In another four cases fresh tissue was available for flow cytometric analysis. A panel of antibodies, which have shown to be reactive in formalin-fixed paraffin embedded tissue, was utilized. This panel included leukocyte common antigen (LCA), pan B-cell marker L26 (CD20), pan T-cell marker UCHL-1 (CD45),

pan T-cell marker CD3, Leu22 (CD43), LeuM1 (CD15), and BerH2 (CD30). These methods have been reported in detail [1].

Outcome End Points and Statistical Analyses

ECOG criteria were used to determine PS and response [7]. Details of the response criteria are provided in our initial report [1]. Toxicity was reported using the guidelines of the National Cancer Institute common toxicity criteria [10]. Febrile neutropenia was defined as any fever $\geq$38°C that occurred when the absolute neutrophil count was $\leq$1,000/μl. All 20 patients enrolled on this study were considered eligible for toxicity, response, and survival analyses.

Comparison of the clinical outcomes from the current NHL-2 study to those from the NHL-1, while not based on a randomized clinical trial, is justified to the extent that the groups of patients in these two studies can be shown to be comparable with respect to potentially confounding variables. The patients in the current NHL-2 trial ($n = 20$) are compared to the patients in the NHL-1 trial ($n = 18$) with respect to clinical measures including demographics; laboratory findings, with respect to known and suggested prognostic factors for AIDS and prognostic factors for lymphoma; and with respect to baseline quality-of-life measures.

For categorical factors, *P* values were calculated using Fisher's exact test; for continuous-valued measures *P* values were calculated using *t*-tests if the underlying distribution was approximately normal and using Wilcoxon (rank-sum) tests otherwise. Median survival durations were compared using Kaplan–Meier method and the log rank test of differences between survival distributions [11,12]. Proportional hazards survival models were evaluated using efficient score statistics. Quality-of-life test scores were treated as approximately normally distributed. CART (Classification And Regression Tree) analysis is a multivariate technique for distinguishing between groups, even if the distinction depends on several factors simultaneously; this was also used to compare the patient groups for the two studies combined. The influence of potential prognostic factors on response and survival was analyzed for the two studies combined. CART analysis was used to identify predictors for febrile neutropenia; proportional hazards models were evaluated for survival times with an individual factor considered useful when adding it to the model accounted for more than 2% of the total variation.

The quality-of-life indicators consisted of the FLIC score and BSI subscales. Details of these instruments have been previously discussed, and the instruments were scored according to published methods [1,13–15]. The FLIC yields a single score with *increases* corresponding with *improvement* in functional well-being [13]. The BSI yields three subscales or scores: General Severity Index (GSI), Positive Symptom Distress Index (PSDI), and the Positive Symptom Total (PST). For each of these, *decreases* correspond to *improvement* in psychological well-being and lessening of distress [14,15]. All these scores were treated as approximately normally distributed. Changes in quality of life were measured from baseline to final evaluation, and these differences were tested using paired *t*-tests.

RESULTS

Patient Characteristics

A total of 19 men and one woman were enrolled, with a median age of 39.5 years (range, 24–51). There were 6 homosexual males, 6 injection drug users, and 6 prisoners (the latter of whom included 3 injection drug users, 2 heterosexual males, and 1 homosexual male) enrolled in this study. Half of the patients enrolled had ECOG PS of 0 or 1 (1 and 9, respectively), and half of the patients had ECOG PS of 2 or 3 (6 and 4, respectively). Sixteen patients (80%) had received nucleoside analog antiretroviral therapy before the diagnosis of lymphoma. Median duration of antiretroviral therapy was 22 months (range, 0–96 months). No patient received prior chemotherapy. The median interval from time of diagnosis of HIV seropositivity to diagnosis of lymphoma was 42 months (range, 1–108 months). The median CD4 lymphocyte count at time of lymphoma diagnosis was 102/μl (range, 3–415/μl) and 10 patients (50%) had CD4 counts <100/μl. All patients met CDC clinical criteria for AIDS, and lymphoma was the AIDS-defining illness in half of the patients. Table III summarizes the clinical variables and quality-of-life scales that were compared between the two study groups (NHL-1 vs. NHL-2), all of which were shown not to be significantly different.

Pathology and Clinical Stage

Lymphomas were classified according to the Working Formulation [8] as follows: diffuse, large cell (intermediate-grade) in 14 (70%) patients; large-cell immunoblastic (high-grade) in 3 (15%); and small noncleaved cell (high-grade) in 3 (15%). Three of the 14 large-cell lymphomas showed high mitotic activity and a prominent starry-sky pattern. The histologic features in these three cases were somewhat intermediate between diffuse large-cell lymphoma not otherwise specified and Burkitt's lymphoma. These three cases were uniformly immunoreactive with pan B-cell marker L26 (CD20) confirming their B-cell lineage. These three lymphomas would currently be classified as high-grade B-cell lymphoma, Burkitt's-like on the basis of the REAL classification [9]. Thus a total of 6 cases (30%) would be regarded as having high-grade histology and 13 (65%) had diffuse large B-cell lymphoma (including 3 with immunoblastic lymphoma) by this classification schema [9].

TABLE III. Comparison of NHL-1 and NHL-2 Studies*

Clinical variable[a]	NHL-1 study (n = 18)	NHL-2 study (n = 20)	NHL-1+2 (n = 38)	P value[b]
Initial information				
Age (years)	35.5 (23–53)	39.5 (24–51)	38.5	0.2
Sex (M/F)	17/1	19/1	36/2	1.0
IDU (user/non-user)	7/11	6/14	13/25	0.7
PS (0+1/2+3)	13/5	10/10	23/15	0.5
Stage (I+II/III+IV)	5/13	3/17	8/30	0.4
A/B symptoms	12/6	13/7	25/13	1.0
Thrush (yes/no)	11/7	12/8	23/15	1.0
Prior OI (yes/no)	5/13	10/10	15/23	0.2
Symptom score[c]	5/13	6/14	11/27	0.6
Laboratory				
CD4 count/μL	73 (2–756)	102 (3–415)	84	1.0
Hemoglobin (g/dL)	11.1 (8.8–15.1)	10.7 (7.5–15.1)	10.8	0.8
WBC count/μL	4.6 (1.8–11.0)	4.5 (2.5–7.8)	4.5	0.8
Platelet count/μL	211 (73–450)	200 (69–348)	200	0.6
Albumin (g/dL)	3.8 (2.0–4.7)	3.5 (2.1–4.5)	3.6	0.7
LDH (IU/L)	294 (166–2387)	262 (137–832)	287	0.6
Response to therapy				
Objective response (CR+PR/all other)	11/7	14/6	25/13	0.4
Febrile neutropenia (yes/no)	11/7	8/12	19/19	0.2
Quality of life (on study scores)				
FLIC	104 (44–74)	103 (73–132)	104	0.4
BSI-GSI	61 (46–80)	66.5 (41–80)	64	0.4
BSI-PSD	56 (44–74)	62.5 (43–73)	60	0.2
BSI-PST	61 (46–75)	63 (41–75)	63	0.6

*Values reported are median (range). Initial information, laboratory, and quality of life values reported are those obtained at baseline.
[a]Continuous measures: median (range); category counts; number (category 1)/number (category 2).
[b]Continuous measures, *t*-test; category counts, Fisher's exact test.
[c]Symptom score: single symptom or none/multiple symptoms (B symptoms, thrush, OI, CD4 < 100/μL, and/or stage III/IV. Abbreviations used: IDU, injecting drug user (user/non-user); PS, performance status; OI, opportunistic infection; and response, CR (complete), PR (partial), and all other, no response, stable disease, progressive disease.

An additional case in the large-cell category showed marked pleomorphism, a sinusoidal growth pattern and was immunoreactive with pan T-cell marker UCHL-1 (CD45RO) and is therefore felt to be consistent with anaplastic large-cell lymphoma (5%) [9].

All patients had measurable disease at time of enrollment. Thirteen (65%) patients had constitutional or B symptoms at the time of diagnosis. The majority of patients (80%) had stage IV disease. The median number of extranodal sites of disease was 2 (range, 0–5). The breakdown of number extranodal sites of disease was as follows: zero sites in 3 patients (15%); one site in 6 patients (30%); two in 3 patients (15%); three in 2 patients (10%); four in 5 patients (25%); and five in 1 patient (5%). Eight patients (40%) had initial bone marrow involvement at time of diagnosis of lymphoma.

Toxicity

Myelotoxicity was the most important toxic effect, with thrombocytopenia more common than neutropenia (Table IV). Severe (grade 3) and life-threatening (grade 4) neutropenia occurred in 51% of cycles: 9 (19%) patients experienced grade 3 and 15 experienced (32%) grade 4. There were 8 episodes (17% of cycles) of febrile

TABLE IV. Summary of Toxicity Due to Chemotherapy by Common Toxicity Criteria [9]*

	Grade[a]				
Toxicity	0	1	2	3	4
Anemia	4	15	15	10	3
WBC	6	8	9	9	15
Platelets	5	9	5	9	19
Fever	20	7	16	4	0
Infection	24	2	11	7	3
Hemorrhage	34	5	4	1	3
Nausea	16	20	8	3	—
Vomiting	21	17	8	1	0
Diarrhea	38	3	3	2	1
Stomatitis	31	11	5	0	0
Skin	32	8	4	3	0
Alopecia	9	22	16	—	—
CNS	36	6	2	2	1
Renal	43	1	3	0	0
Hepatic	37	8	1	1	0
Pulmonary	32	9	5	1	0
Cardiac	42	2	1	2	0

*Data refer to number of patients with stated toxicity encountered for all cycles of therapy initiated (47 cycles). [a]Grade 0, no toxicity; 1, mild; 2, moderate; 3, severe; and 4, life-threatening.

neutropenia [one episode in each of 8 patients (40% of patients)]. Seven patients required hospitalization. Half of the febrile neutropenic episodes occurred during the first cycle; the remainder were evenly divided between the second and third cycles. All were associated with grade 4 neutropenia; the median absolute neutrophil count was 430/μl (range, 40–870/μl). No source of infection was identified in five episodes. In two of these cases febrile neutropenia coincided with rapid lymphoma progression. *P. carinii* pneumonia was identified in two patients, one of whom had stopped taking his PCP prophylaxis and G-CSF during the second cycle of chemotherapy. Methicillin-resistant *Staphylococcus aureus* bacteremia was identified in one case.

There were 28 episodes of grade 3 (9 cycles) and grade 4 (19 cycles) thrombocytopenia, which represented 60% of all cycles of therapy. There were 3 episodes of severe (grade 3) and 1 episode of life-threatening (grade 4) hemorrhage in the current study. Anemia was clinically less pronounced. There were 10 episodes of grade 3 anemia and 3 episodes of grade 4 anemia, which represented 28% of all cycles of therapy.

Other toxicities were less common. Clinically significant nausea and vomiting occurred in 23% and 19% of cycles, respectively, and were manageable in all instances. No episodes of protracted or delayed nausea and vomiting were observed with the oral regimen. Mucosal toxicity was seen in 11% of cycles. Alopecia occurred in one third of cycles and in half of the patients. Clinically significant CNS toxicity and other visceral toxicities were rare.

Therapy was discontinued in 3 patients because of persistent thrombocytopenia beyond the 3-week treatment delay allowable by protocol. There were no episodes of leukopenia that prompted discontinuation of chemotherapy. Dose modifications were made for myelotoxicity. In a single patient, who experienced two episodes of hemorrhagic cystitis (grade 2 renal toxicity), the cyclophosphamide was reduced 50% in the second cycle and discontinued in the third and final cycle of therapy.

There was one treatment-related death. This patient presented on day 8 with fever and WBC count of 400/μl, refused hospitalization, and was treated with oral antibiotics. He died on day 16; no autopsy was performed.

Treatment Results

A total of 47 cycles of therapy were initiated, of which 43.5 were completed, and all were considered assessable for toxicity. The median number of cycles of therapy administered to patients was 2.5 (range, 0.5–3.0 cycles). The overall objective response rate to the oral combination chemotherapy regimen was 70% (95% confidence interval, 50–90%). Six patients (30%) had a complete remission, and 8 (40%) had a partial remission. The median duration of remission was 8.0 months (range, 1.5–58^+ months).

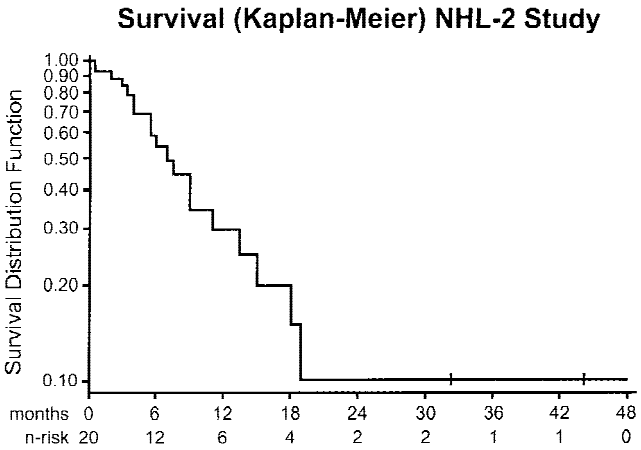

Fig. 1. Kaplan–Meier survival curve in 20 patients with AIDS-related lymphoma (NHL-2 study). Median survival time is 7.3 months (31 weeks).

One patient who was considered to have a partial remission was found to have a pathologic complete remission at time of autopsy. The principal cause of death in this patient was progressive HIV infection. Three other patients were considered to have partial remissions, on the basis of minimal residual lymphadenopathy (mostly 1–2 cm in the cervical or retroperitoneal areas), which did not resolve upon restaging evaluation. In two of these patients, there was pathologic confirmation of resolution of bone marrow involvement. These three patients survived 9, 11, and 19 months. The principal cause of death for all 3 cases was progressive HIV infection, and there was no clinical evidence of progressive lymphoma. Seven patients (35%) completed all 3 cycles of chemotherapy prescribed by protocol. A total of 15 patients (75%) completed two or more cycles of chemotherapy.

Survival, Course, and Causes of Death

The median survival duration for all 20 patients is 7.3 months (31 weeks), with a range of 0.5 to 60^+ months (Fig. 1). The median survival duration of responding patients was 10 months (range, 4–60^+ months), while for all others it was 3.3 months (range, 0.5–5.5 months) [$P < 0.001$]. Autopsies were performed in five of the 18 patients (28%) who died. Two patients were found to have progressive HIV infection and no evidence of lymphoma (pathologic complete remission). The other three patients were found to have progressive lymphoma at postmortem examination. There was no documentation of CNS involvement in these five cases. Of the 18 patients who died, 9 (50%) died of progressive underlying HIV infection. Eight patients (44%) died with progressive lymphoma, and there was one toxic death. Two patients re-

main alive and free of lymphoma at 45^+ and 60^+ months since time of study entry.

Evaluation of the Clinical Role of G-CSF

The current NHL-2 and NHL-1 studies give similar evidence of hematologic toxicity when the incidence of ≥grade 3 toxicity is considered on a per cycle basis; however, comparisons on a per patient basis show differences. There is no significant difference in the incidence of ≥grade 3 neutropenia in the current NHL-2 trial (24 episodes, 51%) when compared to the NHL-1 study (30 episodes, 64%). The number of patients with febrile neutropenia was somewhat lower in the NHL-2 study (40%) than in the NHL-1 study (60%); and on a per cycle basis, the incidence was also lower, but not significantly so (17% in the NHL-2 study versus 28% in the NHL-1 study). There is no difference in the incidence of febrile neutropenia either if the absolute neutrophil count used in the definition is less than 500/μl. The number of patients requiring hospitalization for febrile neutropenia is significantly lower ($P < 0.05$) in the current NHL-2 study (7/20 patients) than in the NHL-1 study (13/18). The length of hospitalization for febrile neutropenia did not differ between studies.

When the incidence of ≥grade 3 thrombocytopenia in the current NHL-2 trial (28 episodes, 60%) is compared to the NHL-1 study (18 episodes, 38%), the difference is significant $P = 0.04$. The incidence (9%) of ≥grade 3 hemorrhage in the current NHL-2 study does not significantly differ from the single episode (2%) of grade 4 hemorrhage observed in the NHL-1 study ($P = 0.2$). The incidence of >grade 3 anemia (28%) in the current NHL-2 study is not significantly different from the 10 episodes of >grade 3 anemia (21%) observed in the NHL-1 trial ($P = 0.5$).

Therapy was discontinued in 3 patients, all of whom had thrombocytopenia that did not resolve within the 3-week period allowable by protocol in the current NHL-2 study. This contrasts with the 7 patients who discontinued treatment in the NHL-1 study [1]. In that study therapy was discontinued in 6 patients because of neutropenia and in the other because of thrombocytopenia. Taken together, the evidence of decreased myelosuppression in the regimen when G-CSF is added (NHL-2 study) is significant. Looked at jointly, the frequencies of discontinuation of therapy due to thrombocytopenia (3 in NHL-2 study vs. 1 in NHL-1 study), due to neutropenia (0 in NHL-2 vs. 6 in NHL-1), myelotoxic death (1 in NHL-2 vs. 1 in NHL-1), and of patients free of myelotoxicity (17 in NHL-2 vs. 10 in NHL-1), the decrease in myelotoxicity in the current NHL-2 study is significant ($P < 0.02$).

Combining data from the two studies (NHL-1+2) shows that anemic patients are at high risk for febrile neutropenia. CART analysis revealed that 85% of patients with hematocrit <28.5% developed febrile neutropenia while only 25% of patients with even low-to-adequate hematocrit (>28.5%) did so.

Quality-of-Life Analysis

Of the 38 patients (NHL-1+2) treated with oral combination chemotherapy, 33 (18 from the current NHL-2 study and 15 from the NHL-1 study) completed at least 2 evaluations: baseline and off-study FLIC and BSI. There was no significant difference between patients from the two studies with respect to baseline scores. With patients from the two studies combined, there was no significant difference between baseline and off-study scores for any of the FLIC or BSI subscale scores. There was, however, a significant change from the baseline to the off-study FLIC scores (*only*) in the subset of patients who experienced febrile neutropenia ($P < 0.05$), reflecting their decline in functional capacity. Patients who did not develop febrile neutropenia evidenced no significant change in FLIC or other scores.

Long-Term Follow-up and Prognostic Factors

At the time of our initial report of oral combination chemotherapy for AIDS-related lymphoma (NHL-1 study), three patients were still alive [1]. Two of these patients died after 27.5 and 53.5 months of follow-up. The former patient initially presented with stage IV large-cell lymphoma with bulky hepatic involvement. He developed a primary CNS lymphoma following a remission duration of 25 months, during which time there was evidence of progressive HIV infection. He died shortly thereafter. The latter patient died without evidence of relapse of lymphoma and with progressive HIV infection. The last patient remains alive after 108^+ months of follow-up.

A total of 38 patients (NHL-1+2) with AIDS-related non-Hodgkin's lymphoma have been treated with oral combination chemotherapy between November 1989 and December 1995, with follow-up through October 1999. The overall objective response rate is 66%, with 34% CR and 32% PR (95% confidence interval, 51–81%). The overall median survival is 7 months (Fig. 2). We have observed a 1-year survival rate of 32% (13 patients), an 18-month survival rate of 21% (9 patients), and a 2-year survival rate of 13% (5 patients).

Nine clinically prognostic factors at time of study entry were available for all 38 patients, with objective response (CR+PR) versus all others (non-responders) determined during the course of follow-up. Proportional hazards regression models with fixed covariates were fitted separately for each of the ten clinical prognostic factors. The absolute value of the correlations among the covariates ranged from 0.02 to 0.60. Among the clinical factors, PS ($P = 0.012$), prior opportunistic infection ($P = 0.014$), B-symptoms ($P = 0.015$), CD4 lymphocyte

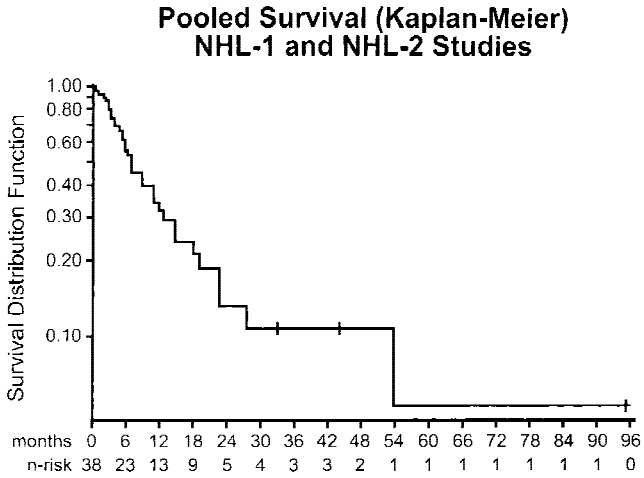

Fig. 2. Kaplan–Meier survival curve in 38 patients (NHL-1+2 studies) with AIDS-related lymphoma and treated with oral combination chemotherapy. Median survival time is 7.0 months. One-year survival rate, 32%; 18-month rate, 21%; and two-year rate, 13%.

count ($P = 0.017$), number extranodal sites of disease ($P = 0.037$), and objective response ($P = 0.006$) were all found to be individually prognostic factors of survival. Patient age, tumor stage, prior thrush, and serum LDH were not found to be statistically prognostic factors of survival.

DISCUSSION

Our results in 38 patients confirm that oral combination chemotherapy consisting of CCNU, etoposide, cyclophosphamide, and procarbazine as prescribed in this regimen is active in the treatment of AIDS-related non-Hodgkin's lymphoma. Important clinical outcome measures include an objective response rate of 66%, of which 34% are complete responses; median survival duration of 31 weeks; and a 13% 2-year survival rate. If the two pathologic CRs confirmed at autopsy (one case from each study) are included in the analysis, the objective complete remission rate is 39%. These results compare favorably to other reports, some of which are summarized in Table V [16–34]. The AIDS Clinical Trials Group (ACTG) reported median survival durations for standard and dose-modified m-BACOD combination chemotherapy of 31 and 35 weeks, respectively, which were not significantly different from one another [17]. The ACTG study is the largest randomized clinical trial of patients with AIDS-related lymphoma.

The 38 patients receiving oral combination chemotherapy comprise a fairly advanced and poor-risk group defined by the following adverse prognostic identified in the ACTG 142 trial: age >35 years, history of injection drug use, stage III or IV disease, and CD4 lymphocyte count less than 100/μl [35]. In the ACTG study patients with zero or one adverse prognostic factor had a 29.5% 3-year survival rate; 2 factors, 16.9%; and 3 or 4 factors, no 3-year survivors were observed [35]. Using these prognostic factors, we found that only a single patient (3%) in our studies had no adverse prognostic factors; 7 (18%) had 1 factor; 11 (29%) had 2 factors; 15 (39%) had 3 factors; and 4 (11%) had 4 factors.

Of the 35 patients who have died, 17 (49%) died from progressive HIV infection or AIDS and free from progressive lymphoma, and 18 (51%, including the 3 toxic deaths) died from progressive lymphoma. This is comparable to the 57% and 70% of patients who died with active lymphoma in the respective standard and dose-modified m-BACOD arms of the ACTG trial [17]. The 32% 1-year and 21% 18-month survival rates with the oral combination chemotherapy regimens are important clinical observations. Furthermore, the 13% 2-year survival rate is in keeping with the generally observed 10–20% freedom from progression or cure of AIDS-related lymphoma reported in other studies, especially in the pre-protease inhibitor therapy era [17,36].

The major clinical toxicity of the oral regimen is undoubtedly myelosuppression, which is comparable to that reported with other regimens. Febrile neutropenia was encountered in 17% of cycles with the use of G-CSF in our current study, which is similar to the 19% of cycles in the initial report of infusional CDE [29]. In a subsequent report of infusional CDE with didanosine, febrile neutropenia occurred in approximately 40% of patients [31]. Although in the modified m-BACOD arm of the ACTG trial, febrile neutropenia occurred in 6% of cycles, only 15% of patients in that trial had bone marrow involvement compared to the 40% of patients in the current NHL-2 study.

The addition of G-CSF to the oral combination chemotherapy regimen may be of value. While this was not a randomized trial, it is justifiable to compare our original group of patients to the current group, who received G-CSF as an adjunctive component to the oral regimen. Both groups of patients are similar when thoroughly evaluated on a variety of clinical parameters. The median and total number of cycles of the same oral regimen was similar for both groups. The addition of G-CSF to the oral regimen, when compared to our initial group of patients, had some clinically meaningful advantages. Most important, the number of hospitalizations for febrile neutropenia was nearly reduced in half ($P < 0.05$). The incidence of neutropenia precluding further chemotherapy because of myelotoxicity was significantly reduced ($P = 0.005$). Although the incidence of ≥grade 3 thrombocytopenia was significantly greater ($P = 0.04$), this did not result in an increased incidence of hemorrhagic complications ($P = 0.2$). Concomitant G-CSF administration provided for fewer interruptions of treatment and the delivery of chemotherapy on schedule. The issue of in-

TABLE V. Summary of Results With Combination Chemotherapy Regimens From Recently Reported Trials in AIDS-Related Non-Hodgkin's Lymphoma*

Regimen	Admin route	No. of patients	CR rate	MST	Long-term survival	CSF prophylaxis	HAART era	Refs.
m-BACOD								
SD	IV bolus	94	52%	31 wks	30%/17%/0% 3-yr	Yes	Pre	17, 35
LD		98	41%	35 wks	by adverse factors[a]			
CDE								
Pre	96-hr CI	48	46%	8.2 months	48% 1-yr	Yes (high-grade; bone marrow+)	Pre	32
Post		60	42%	17.8 months	55% 1-yr		Post	
CHOP								
SD	IV bolus	25	32%	Not available	Not available	No	Post	33
LD		40	30%					
EPOCH	96-hr CI	33	77%	Not reached	72% 2-yr	Yes	Post	34
Oral rx	PO	38	34%	7.0 months	32% 1-yr 13% 2-yr	No	Pre	1, this report

*Abbreviations used: Admin, administration; CR, complete response rate; MST, median survival time; HAART era, pre and post highly active antiretroviral therapy era; SD/LD, standard dose/low dose; rx, regimen; CI, continuous infusion; PO, by mouth.

[a]Three-year survival rates were reported for the ACTG trial for all patients (not by arm of study) by number of adverse prognostic factors: 0 or 1, 30%; 2, 17%; and 3 or 4, 0%; see text for details [35].

corporating a G-CSF schedule into a nitrosourea-based conventional chemotherapy regimen was not problematic. The guidelines for dose modifications and schedule of G-CSF were appropriate as no patient had a relapse of febrile neutropenia during the course of this trial. Our analysis of pretreatment anemia, which is suggestive of an increased risk of subsequent febrile neutropenia, is of interest. Although this is applicable for the limited number of patients treated with oral chemotherapy, we are unaware of any similar analysis with other regimens.

An intriguing observation from this study is the low incidence of CNS relapse or progression. Of the 38 patients (NHL-1+2) treated with oral chemotherapy, only 2 (5%) developed CNS relapse. Both CCNU and procarbazine cross the blood–brain barrier, and their inclusion in the regimen may offer clinical advantages to patients [37,38]. Although the ACTG trial had a similar low rate (3%), all patients in that trial were required to receive CSF prophylaxis with cytosine arabinoside [17].

One potential advantage of the oral regimens used in both the NHL-1 and NHL-2 studies is the maintaining of quality of life. The two quality-of-life instruments were chosen because they are rapid, self-administered, and already validated in cancer patients. The FLIC assesses the functional status of activities of daily living [13]; and the BSI assesses the psychological status of the patient [14,15]. The functional status observed in our patients using the FLIC scale is comparable to that seen in HIV-uninfected patients with regionally advanced or metastatic solid tumors by comparing pretreatment scores [13,39,40]. The BSI scores observed in our patients suggest a moderate level of psychological distress at the time of study entry, which is comparable as well to that observed in other solid tumor patients [41–43]. An unexpected observation was the lack of any consistent pattern of deterioration from baseline until off-study, with the exception of the clear deterioration ($P < 0.05$) in functional status (FLIC) of patients with febrile neutropenia. These results imply that in the absence of febrile neutropenia there is no significant functional or psychological deterioration in patients with AIDS-related lymphoma during therapy.

In summary, the advantages of oral combination chemotherapy for AIDS-related lymphoma are straightforward. Administration of the oral regimen has resulted in one-third of patients surviving one year, 13% two years, and half of the 38 patients surviving free from progression of their lymphoma. These results are comparable to those observed with other more traditional intravenous combination chemotherapy regimens used in this setting. This regimen is efficacious and considerate of patient quality-of-life issues. The addition of G-CSF to the regimen decreases the frequency of hospitalization for febrile neutropenia and discontinuation of chemotherapy due to leukopenia.

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