REVIEW ARTICLE

Drugs 1999; 58 Suppl. 3: 99-107
0012-6667/99/0003-0099/$04.50/0

Oral Combination Chemotherapy in the Management of AIDS-Related Lymphoproliferative Malignancies

Scot C. Remick,[1] *Nell Sedransk,*[2] *Richard Haase,*[3] *Mark Craffey,*[1] *Neepa Subramanian,*[2] *Afshin Dowlati,*[1] *Tipu Nazeer,*[4] *Carm Ramnes,*[5] *Christina Blanchard,*[6] *David Mastrianni,*[6] *Lodovicco Balducci,*[7] *John Horton*[7] and *John C. Ruckdeschel*[7]

1 Division of Hematology/Oncology, Case Western Reserve University, and the Ireland Cancer Center at University Hospitals of Cleveland, Cleveland, Ohio, USA
2 Department of Statistics, Case Western Reserve University, Cleveland, Ohio, USA
3 Department of Psychology, State University of New York at Albany, Albany, New York, USA
4 Department of Pathology and Laboratory Medicine, Albany Medical College, Albany, New York, USA
5 Division of HIV Medicine, Albany Medical College, Albany, New York, USA
6 Division of Hematology and Medical Oncology, Albany Medical College, Albany, New York, USA
7 H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida, USA

Abstract

An oral combination chemotherapy regimen initially developed for AIDS-related non-Hodgkin's lymphoma includes lomustine (CCNU), etoposide, cyclophosphamide, and procarbazine. This regimen takes advantage of oral administration, the *in vitro* synergy of these drugs and their first-line efficacy in lymphoma, and the ability of lomustine and procarbazine to cross the blood-brain barrier. This regimen was used to treat 38 patients with AIDS-related non-Hodgkin's lymphoma. The overall objective response rate was 66% (34% complete response rate) with a 5% CNS relapse rate, and a median survival duration of 7.0 months. One-third of the patients survived for 1 year, 11% for 2 years, and half of the patients survived free from progression of their lymphoma. On the basis of these results, this oral regimen was modified and administered to 5 patients with AIDS-related primary CNS lymphoma as part of a sequential combined-modality chemotherapy and radiation regimen. Rapid progression of CNS disease was observed in this group of patients, with a median survival duration of 1.0 month. The identical regimen was administered to 7 patients with AIDS-related Hodgkin's disease: we observed a 71% partial remission rate and a median survival duration of 7.0 months. Myelosuppression remains the most significant clinical toxicity. Our results with this oral regimen appear comparable to those of standard intravenous combination chemotherapy regimens in patients with AIDS-related non-Hodgkin's lymphoma.

In 1989, we set out to design and evaluate an oral-based combination chemotherapy regimen for patients with AIDS-related non-Hodgkin's lymphoma (NHL). This approach is pragmatic and theoretically has several advantages over more traditional intravenous combination chemotherapy regimens. Principal advantages of an entirely oral-based combination chemotherapeutic approach in this setting include ease of administration and favourable pharmacoeconomic and quality-of-life outcomes. Treatment is self-administered, and consequently there is no medical risk to personnel engaged in the administration of cytotoxic chemotherapy. Chemotherapy administration costs and charges are less. Outpatient care is facilitated and time invested in chemotherapy administration is markedly reduced. These issues are addressed throughout this supplement.[1] Given this backdrop, a brief overview of the treatment of AIDS-related NHL and the rationale for an oral combination chemotherapy regimen are discussed. Our experience with this regimen in various AIDS-related lymphoproliferative malignancies, including systemic NHL, primary CNS lymphoma and Hodgkin's disease, is summarised. Finally, future directions and plans for this oral regimen are also discussed.

1. Brief Overview of AIDS-Related NHL

In general, AIDS-related NHL is characterised by higher grade (40 to 60%), greater predilection for extranodal disease (80%), more advanced clinical stage (60 to 70% stage III/IV), an aggressive clinical course, and shortened survival (median, 7 to 8 months) compared with lymphomas in HIV-seronegative patients.[2-5] At time of presentation the median CD4+ lymphocyte count is 100 cells/μl.[4] The poor prognosis of AIDS-related lymphoma initially resulted in the evaluation of more aggressive and dose-intensive combination chemotherapy regimens. Early results were dismal, regimens were poorly tolerated, and there was a trend towards shortened survival.[6,7] More traditional NHL combination chemotherapy regimens were then evaluated in conjunction with antiretroviral therapy, including the incorporation of colony-stimulating factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which is known to upregulate HIV viral replication,[8] and the use of various CNS prophylaxis strategies because of the proclivity of AIDS-related lymphoma to disseminate or relapse in the CNS.[9] Complete responses (CR) ranged from 20 to 60%, with median survival durations of 4 to 7 months.[2-4]

In June 1997, the AIDS Clinical Trials Group (ACTG) reported the largest randomised clinical trial in 198 patients with AIDS-related NHL. The ACTG 142 study compared standard dose (SD) methotrexate, bleomycin, doxorubicin (adriamycin), cyclophosphamide, vincristine, and dexamethasone (m-BACOD) plus GM-CSF with a dose-modified [low dose (LD)] m-BACOD regimen.[4] All patients received intrathecal cytarabine (cytosine arabinoside) for meningeal prophylaxis during the first cycle of chemotherapy. The results of this study confirmed that the dose-modified regimen was associated with less haematological toxicity and was better tolerated than SD m-BACOD. Efficacy in the 2 arms was equivalent, with a 39% CR with LD versus a 52% CR with SD ($p = 0.56$); median survival durations were 35 weeks for LD and 31 weeks for SD ($p = 0.25$). Poor prognostic factors identified included age >35 years; history of intravenous drug use; stage III/IV disease; and, most importantly, a CD4+ lymphocyte count of <100 cells/μl.[4-10] A 3% CNS relapse rate was observed.

Although the results of the ACTG 142 study demonstrated the advantages of a modified-dose regimen, the optimal regimen for AIDS-related NHL remains undefined. The longest median survival duration reported for AIDS-related NHL in a cohort of 46 patients was 18 months.[11-13] These patients were treated with a 96-hour continuous infusion of cyclophosphamide-doxorubicin-etoposide; this regimen is presently being further evaluated by the Eastern Cooperative Oncology Group in both HIV-seronegative and -seropositive patients. The overall CR rate with this regimen was

57%.[11-13] It is important to note that on the basis of a review of recent clinical trial data, 10 to 20% of patients with AIDS-related NHL may be cured (i.e. survive free from progression of their lymphoma).[2-4,14] Of patients with good prognostic factors at presentation, up to 30% may survive for 3 years, and selected patients may be appropriate candidates for more traditional (e.g. intravenous) or aggressive cytotoxic chemotherapy.[4,10]

2. Rationale for an Oral Combination Chemotherapy Regimen in AIDS Lymphoma

An oral combination chemotherapy regimen including lomustine (CCNU), etoposide, cyclophosphamide, and procarbazine has been developed.[15] The rationale for this regimen is straightforward and takes advantage of the oral administration of these agents. All of the drugs in this regimen are active in lymphoma when used as single agents, with response rates ranging from 10 to 40%.[16-19] These agents have been incorporated to varying degrees into front-line combination chemotherapy regimens for *de novo* intermediate and high grade lymphomas.[20] Combination chemotherapy is believed to be superior to single agents in *de novo* lymphoma.[21] Both lomustine and procarbazine cross the blood-brain barrier, a quality that may be of value given the relatively frequent involvement of the CNS in HIV-related lymphoma.[19,22,23] Etoposide has demonstrable synergy with cyclophosphamide and nitrosoureas in laboratory models.[23,24] Corticosteroids were purposely omitted from the regimen because of their additional immunosuppressive effects and possible promotion of tumour growth in patients with Kaposi's sarcoma.[25-29] As cardiomyopathy has been well characterised in HIV-infected patients, this regimen avoids the potential cardiotoxicity of doxorubicin-based regimens.[30,31]

3. Systemic NHL

A total of 38 patients with AIDS-related intermediate and high grade NHL have been treated with an oral combination chemotherapy regimen (table I).[15,32] Patients received the following dose and schedule of chemotherapy: lomustine 100 mg/m^2 orally on day 1, on odd treatment cycles; etoposide 200 mg/m^2 orally on days 1 through 3; and cyclophosphamide and procarbazine, 100 mg/m^2 each orally on days 22 through 31. Cycles were repeated every 6 weeks.[15,32] In our second study, the duration of treatment was shortened from 5 to 3 cycles and granulocyte colony-stimulating factor (G-CSF) was added in the hope of lessening myelosuppression, according to the following schedule: 5 μg/kg subcutaneously, days 5 through 21 and days 33 through 42 (see table II for dose modifications based on haematological parameters).[32]

Table I. Oral combination chemotherapy regimen for patients with AIDS-related non-Hodgkin's lymphoma

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

a All drugs administered orally.

b Lomustine (CCNU) administered during cycle numbers 1, 3, and 5. Cycles are repeated every 6 weeks.

c G-CSF is administered subcutaneously until absolute neutrophil count is >10 000 cells/μl beyond the nadir period, which coincides with days 15 and 36 of each portion of the treatment cycle.

G-CSF = granulocyte colony-stimulating factor.

The overall toxicity of this regimen compares favourably with that of others. Myelosuppression was the most frequent and severe toxicity encountered, with leucopenia being more pronounced than thrombocytopenia; there was a 57% incidence of ≥ grade 3 neutropenia and a 49% incidence of ≥ grade 3 thrombocytopenia with this oral chemotherapy regimen. A total of 21 episodes of febrile neutropenia (21% of treatment cycles) occurred. The incidence of clinically significant (≥ grade 2) nausea, vomiting, diarrhoea, and stomatitis was low with this regimen.[15,32]

The addition of G-CSF to the regimen decreased the frequency of hospitalisation for febrile neutropenia and decreased the discontinuation of

Table II. Dose modifications based on haematological parameters [dose modifications made on the day of therapy (i.e. days 1 and 22 only)]

WBC count (cells/μl)	Platelet count (cells/μl)	Dose (%)[a]	G-CSF dose (μg/kg)[b]
>4000	>100 000	100	5
3000-3999	>100 000	100	5
3000-3999	75-99 999	75	5
1500-2999	50-74 999	50	10
<1499	<49 999	0	10

a All drugs. For patients who required hospitalisation for fever and neutropenia, the next cycle was administered upon recovery at a 50% dose reduction compared with the preceding cycle, provided neutropenia was attributable to cytotoxic chemotherapy; afterwards, 25% dose escalations were made up to the 100% dose.

b G-CSF was usually administered in 300μg (5 μg/kg) or 480μg (10 μg/kg) doses to facilitate patient administration. During G-CSF administration, complete blood counts with differential were monitored twice weekly; if at any time during the postnadir period (beyond day 15 and day 36) the ANC was ≥10 000 cells/μl, G-CSF was discontinued.

G-CSF = granulocyte colony-stimulating factor; **WBC** = white blood cell.

chemotherapy because of leucopenia.[32] Thrombocytopenia, however, was more severe. The incidence of grades 3 and 4 leucopenia, febrile neutropenia, and the durations of hospitalisation for febrile neutropenia were similar in the 2 separate studies of patients treated with and without G-CSF.[32] The median number of cycles received was 2.5. The overall objective response rate with this regimen was 66% (CR 34%), with a 5% CNS relapse rate and a median survival duration of 7.0 months.[15,32] In addition, one-third of the patients survived for 1 year, 11% for 2 years, and half of all patients survived free from progression of their lymphoma. Three patients from this cohort remain alive at 30, 41, and 92 months. These results are comparable to those reported for intravenous combination chemotherapy regimens.

In the second generation study of the oral combination chemotherapy regimen, objective responses were observed in 13 of 20 patients (65%) upon completion of the first cycle of chemotherapy, and another patient responded after the second cycle, giving an overall response rate of 70%.[32] Restaging evaluation was performed in this study after the first cycle of therapy (6 weeks), which was considered induction treatment. The majority of these responses were partial remissions, since pathological restaging of the bone marrow in patients with initial bone marrow involvement was performed at the end of treatment (3 cycles of therapy). This was applicable in 2 patients (10%), who were found to have CRs with restaging bone marrow examination. Response was not evaluable or progressive disease was found in the 6 remaining patients (30%) at the time of restaging after the first course of treatment. In addition, documented objective and durable responses (including pathological CR) have been observed in patients receiving only one cycle of the oral chemotherapy regimen and with dose modifications prescribed by protocol.[32]

It is of interest that, among the 38 patients we have treated, 30 (79%) had 2 or more adverse prognostic factors, as described in the recent follow-up of the ACTG 142 trial.[4] The breakdown of adverse prognostic factors in our patients was as follows: age >35 years, 26 patients (68%); history of intravenous drug use, 13 patients (34%); CD4+ lymphocyte count <100 cells/μl, 21 patients (55%); and stage III/IV disease, 30 patients (79%).

4. Primary CNS Lymphoma

In our initial trial of oral combination chemotherapy in patients with AIDS-related intermediate and high grade NHL, only 1 of 18 patients (6%) developed CNS disease following treatment.[15] At time of enrolment, patients were required to have no evidence of CNS involvement, on the basis of the absence of clinical signs and symptoms, negative radiographic studies of the brain, and negative CSF cytology. As discussed above, 2 of the 4 agents in the combination regimen are known to cross

the blood-brain barrier, which might provide a theoretical advantage for their inclusion in the regimen to prevent CNS relapse or progression. Subsequently, these observations were confirmed in our second trial of the identical oral combination regimen in which only a single patient out of 20 experienced CNS progression,[32] giving an overall CNS progression rate in both studies of 5% (2 of 38 patients).

On the basis of these initial results, we embarked on a sequential combined-modality chemotherapy and radiation trial in patients with AIDS-related primary CNS lymphoma (table III). Patients with biopsy-proven AIDS-related CNS lymphoma receive a 6-week course of lomustine and procarbazine. The schedule is as follows: lomustine 100 mg/m^2 orally on day 1 and procarbazine 100 mg/m^2 orally on days 1 through 10 and days 22 through 31, with G-CSF support. This is followed by a course of whole-brain radiotherapy. The radiation dose is administered in a standard fashion to include the whole brain and meninges. The total dose administered is 50.4Gy in 28 fractions with a daily fraction size of 1.8Gy. Both the right and left lateral fields are treated daily.

To date, a total of 5 patients have been treated with this regimen. The oral regimen is reasonably well tolerated; however, we have observed very rapid CNS progression. The median survival for these 5 patients is 1.0 month (range, 0.75 to 3.5 months).[33] No patient has yet been able to complete the sequential chemotherapy and radiotherapy prescribed by protocol. This approach therefore must be regarded as investigational. Other studies used concurrent chemotherapy and radiotherapy in this setting. These results, which must be considered preliminary, reveal survival durations of 1 to 3.5 months.[34-36]

Radiotherapy historically has been the primary treatment modality for primary CNS lymphoma. It appears that combined-modality chemotherapy and radiation in HIV-seronegative/indeterminate CNS lymphoma improves median survival by approximately 3 years and is the preferred approach.[37] This clearly must be regarded as an investigational approach in the HIV setting, and trials are currently underway to define feasibility, toxicity, and efficacy. In the absence of a clinical trial, we generally offer definitive radiation therapy or sequential combined-modality therapy (i.e. one cycle of chemotherapy followed by radiation in 'good-risk' patients), and attempt to wean patients off corticosteroids as rapidly as possible.

5. Hodgkin's Disease

It has recently been established that the incidence of Hodgkin's disease is increased in HIV-infected patients.[38-40] This tumour has been well characterised, especially in injecting drug users in Europe.[41] Several features of the natural history of this disease in this setting are worthy of comment. The majority of patients present with stage

Table III. Characteristics of patients treated with oral chemotherapy[a]

	NHL-1[15]	NHL-2[32]	PCL[33]	HD[33,34]
No. of patients	18	20	5	7
No. of males/females	17/1	19/1	4/1	7/0
Median age (years)	35	39.5	42	39
ECOG PS [no. of patients (%)]				
0/1	13 (72)	10 (50)	4 (80)	5 (71)
2/3	5 (28)	10 (50)	1 (20)	2 (29)
Median CD4+ (cells/μl)	73	102	4	180
No. of patients (%) with stage III/IV disease	13 (72)	17 (85)	0[b]	6 (86%)

a All patients received oral combination chemotherapy for AIDS-related lymphoproliferative disease: non-Hodgkin's lymphoma (NHL), primary CNS lymphoma (PCL), and Hodgkin's disease (HD). Patients with PCL received sequential radiation.

b All patients had stage IE PCL.

ECOG = Eastern Cooperative Oncology Group; **PS** = performance status.

III and IV disease (often with extranodal disease) and, as a result, systemic chemotherapy is the mainstay of treatment.[41,42] The most common histological subtypes are mixed-cellularity and lymphocyte-depleted, and mediastinal involvement occurs less frequently than in *de novo* Hodgkin's disease. The frequency of Epstein-Barr virus genome expression appears to be higher in HIV-related Hodgkin's disease compared with *de novo* disease. Current treatment approaches have generally focused on traditional chemotherapy for Hodgkin's disease, with the greatest experience reported for the doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) regimen. The complete remission rate is about 50%, and median survival is approximately 18 months.[42] Although the optimal chemotherapy regimen remains to be established, a variety of regimens are currently under investigation. It also remains to be established whether a dose-modified approach similar to that for NHL is appropriate, and prospects for progression-free and long term survival need to be identified.

We have treated 7 patients with AIDS-related Hodgkin's disease using the all-oral NHL regimen outlined in table I.[43] The rationale for studying this particular combination in Hodgkin's disease is straightforward. All of the drugs have known single agent activity in Hodgkin's disease, with responses ranging from 20 to 60%.[23,44-47] All of these agents have been incorporated to varying degrees into front-line and salvage combination chemotherapy for *de novo* Hodgkin's disease.[48-51] This approach also capitalises on the advantages of an oral regimen, as discussed at the outset.

To date, our experience has been encouraging. We have observed 5 partial remissions in 7 patients (71%), with a median survival duration of 7.0 months (range, 2.5 to 43 months).[33,43] There appears to be no difference in the toxicity of this regimen between patients with AIDS-related Hodgkin's disease and NHL patients. We continue to recruit patients to this particular study to further define the toxicity profile and efficacy of the oral regimen in this setting.

6. Future Directions

Our experience with an oral combination chemotherapy regimen consisting of lomustine, etoposide, cyclophosphamide, and procarbazine in 50 patients with various AIDS-related lymphoproliferative diseases has been favourable. The efficacy of this regimen in NHL and Hodgkin's disease appears comparable to that reported for traditional intravenous combination chemotherapy regimens. Overall median survival for NHL was 7 months, with 1.0 month for CNS lymphoma, and 7.0 months for Hodgkin's disease (fig. 1).[33] Surprisingly, patient compliance has not been a major issue. This, however, will need to be further evaluated, as the majority of patients have been treated prior to the protease inhibitor-based combination highly active antiretroviral therapy (HAART) era.

Given our initial experience with this regimen, we are in the midst of launching an international dose-modified oral combination chemotherapy regimen for patients with HIV-associated NHL based on the recent follow-up of the ACTG 142 study and collaborating institutions in Uganda and Kenya. In this particular trial, patients in the United States will receive a 50% dose reduction of all chemotherapy agents in the regimen.

We have further evaluated the toxicity profile and efficacy of the identical oral combination chemotherapy regimen in a limited number of elderly patients with *de novo* NHL. Many elderly patients are not suitable candidates for doxorubicin-based combination chemotherapy, and there may be advantages in avoiding high dosages of corticosteroids in these patients as well. Myelotoxicity remains the most significant clinical toxicity. Further dose modification of the oral regimen, perhaps using a more protracted dosage schedule for etoposide, may be appropriate.

In summary, oral combination chemotherapy in the management of AIDS-related lymphoproliferative diseases is feasible, can be administered with acceptable clinical toxicity, and offers many practical advantages compared with standard intravenous chemotherapy regimens. Further dose modi-

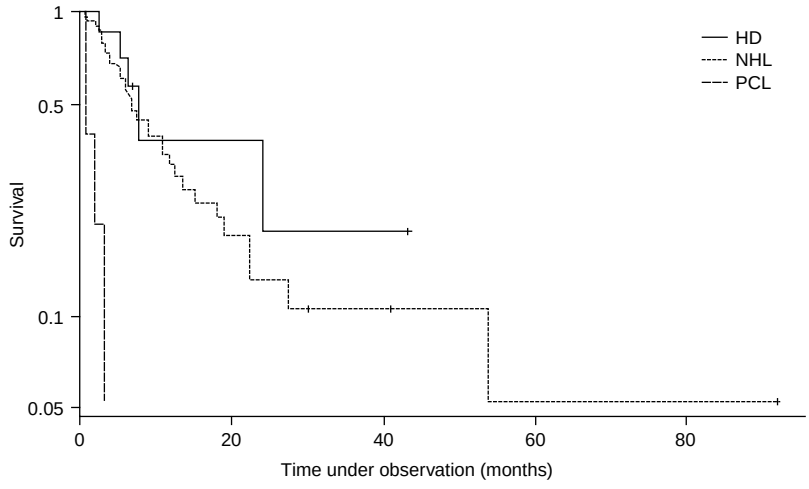

Fig. 1. Kaplan-Meier survival curves for AIDS-related non-Hodgkin's lymphoma (NHL): 38 patients, median survival of 7.0 months; primary CNS lymphoma (PCL): 5 patients, median survival of 1.0 month; and Hodgkin's disease (HD): 7 patients, median survival of 7.0 months.

fication of the oral regimen in this setting may well improve the therapeutic index of the regimen and significantly lessen the myelosuppression. Ongoing studies of this regimen are planned. In appropriate patients who are highly desirous of an oral treatment approach for a variety of reasons, this regimen is a suitable alternative to more traditional intravenous chemotherapy regimens.

Acknowledgements

This work was supported in part by AmFAR project grant number 600027-9-CTR; AmFAR operating grant number 400069-11-GCR; two clinical research grants from Amgen Inc., Thousand Oaks, CA; and NIH grant number AI 30883.

References

1. Greco FA. Introduction to the first comprehensive conference on oral chemotherapy for the treatment of patients with cancer. Drugs 1999; 58 Suppl. 3: 35-41
2. Freter CD. Acquired immunodeficiency syndrome associated lymphoma. NCI Monogr 1990; 10: 45-54
3. Remick SC. AIDS-related non-Hodgkin's lymphoma. Cancer Control 1995; 2: 97-103
4. Kaplan LD, Straus DJ, Testa MA, et al. Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. N Engl J Med 1997; 336: 1641-8
5. Ziegler JL, Beckstead JA, Volberding PA, et al. Non-Hodgkin's lymphoma in 90 homosexual men: relation to generalized lymphadenopathy and acquired immunodeficiency syndrome. N Engl J Med 1984; 311: 565-70
6. Kaplan LD, Abrams DI, Feigal E, et al. AIDS-associated non-Hodgkin's lymphoma in San Francisco. JAMA 1989; 261: 719-24
7. Gill PS, Levine AM, Krailo M, et al. AIDS-related malignant lymphoma: results of prospective treatment trials. J Clin Oncol 1987; 5: 1322-8
8. Kaplan LD, Kahn JO, Crowe S, et al. Clinical and virologic effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. J Clin Oncol 1991; 9: 929-40
9. Levine AM, Wernz JC, Kaplan L, et al. Low-dose chemotherapy with central nervous system prophylaxis and zidovudine maintenance in AIDS-related lymphoma. A prospective multi-institutional trial. JAMA 1991; 266: 84-8
10. Straus DJ, Huang J, Testa MA, et al. Prognostic factors in the treatment of HIV-associated non-Hodgkin's lymphoma (HANHL): Analysis of ACTG 142 (low-dose *vs* standard-dose m-BACOD + GM-CSF). J Acquir Immune Defic Syndr Human Retrovirol 1997; 14: 38A
11. Sparano JA, Wiernik PH, Strack M, et al. Infusional cyclophosphamide, doxorubicin and etoposide in human immunodeficiency virus and T-cell leukemia virus type 1-related non-Hodgkin's lymphoma: a highly active regimen. Blood 1993; 81: 2810-5
12. Sparano JA, Wiernik PH, Strack M, et al. Infusional cyclophosphamide, doxorubicin and etoposide in HIV-related non-

Hodgkin's lymphoma: a follow up report of a highly active regimen. Leuk Lymphoma 1994; 14: 263-71
13. Sparano JA, Wiernik PH, Hu X, et al. Pilot trial of infusional cyclophosphamide, doxorubicin and etoposide plus didanosine and filgrastim in patients with human immunodeficiency virus-associated non-Hodgkin's lymphoma. J Clin Oncol 1996; 14: 3026-35
14. Davis AJ, Goldstein D, Milliken S. Long term follow-up of CEOP in the treatment of HIV-related non-Hodgkin's lymphoma (NHL). Aust N Z J Med 1998; 28: 28-32
15. Remick SC, McSharry JJ, Wolf BC, et al. Novel oral combination chemotherapy in the treatment of intermediate-grade and high-grade AIDS-related non-Hodgkin's lymphoma. J Clin Oncol 1993; 11: 1691-702
16. Carbone P, Spurr C. Management of patients with malignant lymphoma: a comparative study with cyclophosphamide and vinca alkaloids. Cancer Res 1968; 28: 811-22
17. EORTC, Clinical Screening Group. Epipodophyllotoxin (VP-16-213) in treatment of acute leukaemias, haematosarcomas and solid tumours. BMJ 1973; 3: 199-202
18. Stolinsky DC, Solomon J, Pugh RP, et al. Clinical experience with procarbazine in Hodgkin's disease, reticulum cell sarcoma and lymphosarcoma. Cancer 1970; 26: 984-90
19. Wasserman T, Slavik M, Carter S. Review of CCNU in clinical cancer therapy. Cancer Treat Rev 1974; 1: 131-51
20. Klimo P. Chemotherapy for aggressive non-Hodgkin's lymphoma. In: DeVita V, Hellman S, Rosenberg S, editors. Updates: cancer: principles and practice of oncology. Vol. 1. Philadelphia: Lippincott, 1988: 1-12
21. Lowenbraun S, DeVita V, Serpick A. Combination chemotherapy with nitrogen mustard, vincristine, procarbazine and prednisone in lymphosarcoma and reticulum cell sarcoma. Cancer 1970; 25: 1018-25
22. Spivack SO. Drugs 5 year later: procarbazine. Ann Intern Med 1974; 81: 795-800
23. Dombernowsky P, Nissen N. Combination chemotherapy with 4' demethylepipodophyllotoxin-9-(4,6-0-ethylidine-β-D-glucopyranoside) VP-16-213 (NSC 11141540) in L-1210 leukemia. Eur J Cancer 1976; 12: 181-8
24. Burchenal J, Lokys L, Turkevich J, et al. Rationale of combination chemotherapy. In: Prestoyko A, Crookes S, Carter S, editors. Cisplatin: Current status and new developments. New York: Academic Press, 1980: 113-23
25. Garber EK, Fan PT, Bluestone R. Realistic guidelines of corticosteroid therapy in rheumatic disease. Semin Arthritis Rheum 1981; 11: 231-56
26. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989; 11: 954-63
27. Gill PS, Loureiro C, Bernstein-Singer M, et al. Clinical effect of glucocorticoids on Kaposi sarcoma related to the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 1989; 110: 937-40
28. Real FX, Krown SE, Koziner B. Steroid-related development of Kaposi's sarcoma in a homosexual man with Burkitt's lymphoma. Am J Med 1986; 80: 119-22
29. Schulhafer EP, Grossman ME, Fagin G, et al. Steroid-induced Kaposi's sarcoma in a patient with pre-AIDS. Am J Med 1987; 82: 313-7
30. Cohen IS, Anderson DW, Virmani R, et al. Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. N Engl J Med 1986; 315: 628-30
31. Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. J Am Coll Cardiol 1989; 13: 144-54
32. Remick SC, Bibighaus MR, Reddy M, et al. Oral combination chemotherapy (CT) in conjunction with filgrastim (G-CSF) in the treatment of AIDS-related non-Hodgkin's lymphoma (NHL). J Acquir Immune Defic Syndr Human Retrovirol 1997; 14: 37A
33. Remick SC, Haase RF, Reddy M, et al. Prospective evaluation of clinical prognostic factors and quality of life (QOL) indices using the Functional Living Index – Cancer (FLIC) and Brief Symptom Inventory (BSL) in patients with AIDS-related neoplasms. J Acquir Immune Defic Syndr Human Retrovirol 1998; 17: 32A
34. Forsyth PA, Yahalom J, DeAngelis LM. Combined modality therapy in the treatment of primary central nervous system lymphoma in AIDS. Neurology 1994; 44: 1473-9
35. Remick SC, Diamond C, Migliozzi JA, et al. Primary central nervous system lymphoma in patients with and without the acquired immune deficiency syndrome. A retrospective analysis and review of the literature. Medicine (Baltimore) 1990; 69: 345-60
36. Baumgartner JE, Rachlin JR, Beckstead JH, et al. Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. J Neurosurg 1990; 73: 206-11
37. Fine HA, Mayer RJ. Primary central nervous system lymphoma. Ann Intern Med 1993; 119: 1093-104
38. Lyter DW, Bryant J, Thackeray R, et al. Incidence of human immunodeficiency virus-related and nonrelated malignancies in a large cohort of homosexual men. J Clin Oncol 1995; 13: 2540-6
39. Rabkin CS. Epidemiology of malignancies other than Kaposi's sarcoma and non-Hodgkin's lymphoma in HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 14: 12A
40. Grulich A, Wan X, Law M, et al. Rates of non-AIDS defining cancers in people with AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 13: 18A
41. Tirelli U, Errante D, Dolcetti R, et al. Hodgkin's disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and Tumors. J Clin Oncol 1995; 13: 1758-67
42. Levine AM. HIV-associated Hodgkin's disease. Biologic and clinical aspects. Hematol Oncol Clin North Am 1996; 10: 1135-48
43. Remick SC, Doshi S, Bibighaus M, et al. Oral combination chemotherapy (CT) in the treatment of AIDS-associated Hodgkin's disease (HD). Proc Am Soc Clin Oncol 1996; 15: 307A
44. Gershwin MF, Goetzl EJ, Steinberg AD. Cyclophosphamide: use in practice. Ann Intern Med 1974; 80: 531-40
45. Issell BF, Crooke ST. Etoposide (VP-16-213). Cancer Treat Rev 1979; 6: 107-24
46. O'Dwyer PJ, Leyland-Jones B, Alonso MT, et al. Etoposide (VP-16-213). Current status of an active anticancer drug. N Engl J Med 1985; 312: 692-700
47. Wiernik PH. Chemotherapy of Hodgkin's disease. In: DeVita Jr VT, Hellman S, Rosenberg SA, editors. Updates: Cancer. Principles and practice of oncology. Vol. 2. Philadelphia: Lippincott, 1988: 1-12

48. DeVita Jr VT, Serpick A, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970; 73: 881-95
49. DeVita Jr VT, Simon RM, Hubbard SM, et al. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP-treated patients at the National Cancer Institute. Ann Intern Med 1980; 92: 587-95
50. Bakemeier RF, Anderson JR, Costello W, et al. BCVPP chemotherapy for advanced Hodgkin's disease: evidence for greater duration of complete remission, greater survival, and less toxicity than with a MOPP regimen. Results of the Eastern Cooperative Oncology Group study. Ann Intern Med 1984; 101: 447-56
51. Buzaid AC, Lippman SM, Miller TP. Salvage therapy of advanced Hodgkin's disease. Critical appraisal of curative potential. Am J Med 1987; 83: 523-32

Correspondence and reprints: Dr *Scot C. Remick,* Division of Hematology/Oncology, Case Western Reserve University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106, USA.
E-mail: scr@po.cwru.edu