Second-Line Chemotherapy in Human Immunodeficiency Virus-Related Non-Hodgkin's Lymphoma

Evidence of Activity of a Combination of Etoposide, Mitoxantrone, and Prednimustine in Relapsed Patients

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Supported by grants of Associazione Italiana per la Ricerca sul Cancro (AIRC), Milan, Italy, 1994 and VII AIDS Project, Istituto Superiore di Sanità (ISS), Rome, Italy, 1994.

The authors gratefully acknowledge the assistance of Clifford Gunthel, M.D., of Atlanta, Georgia, for reviewing this manuscript. They also thank Dr. Maddalena Mosconi for help with the manuscript.

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Received October 19, 1995; revision received January 29, 1996; accepted January 29, 1996.

BACKGROUND. There is very little experience reported in the literature on the treatment of patients with relapsed or resistant human immunodeficiency virus-related non-Hodgkin's lymphoma (HIV-NHL). We performed a prospective study to evaluate the feasibility and activity of a second-line chemotherapy regimen consisting of etoposide, mitoxantrone, and prednimustine (VMP) in this setting.

METHODS. Twenty-one patients were consecutively treated. Thirteen patients were resistant to primary chemotherapy and 8 patients had relapsed after their first complete remission (CR). Etoposide and prednimustine were both given orally at doses of 80 mg/m^2 daily for 5 days, and mitoxantrone was given intravenously at a dose of 10 mg/m^2 on Day 1; the cycles were repeated every 3 weeks.

RESULTS. Nineteen of 21 patients were evaluable for response. The median number of cycles administered was 2 (range, 1–5). A CR occurred in 5 of 19 patients (26%; exact 95% confidence interval; 9–51%). Four of these CRs were observed in the 7 evaluable relapsed patients. Of 45 cycles evaluable for toxicity, severe neutropenia ($< 500/\mu L$) occurred in 19 (42%) cycles and severe thrombocytopenia ($< 25{,}000/\mu L$) in 6 (13%) cycles. One toxic death occurred due to sepsis during neutropenia. The overall median survival was 2 months (range, < 1–13 months); the median survival time for the 5 patients with CR (13 months; range, 6–13 months) was statistically significantly longer than that observed in patients without CR (2 months; range, < 1–7 months).

CONCLUSIONS. Although the overall prognosis of patients with resistant or relapsed HIV-NHL is very poor, palliative therapy with VMP can be effective and relatively safe in the latter group. Prolonged survival has been observed in some patients who had relapsed after initial chemotherapy. ***Cancer* 1996; 77:2127–31.**

KEYWORDS: HIV, non-Hodgkin's lymphoma, second-line treatment, survival.

Although the overall prognosis for patients with human immunodeficiency virus-related non-Hodgkin's lymphoma (HIV-NHL) is poor, a subgroup of patients with HIV-NHL, i.e., those with favorable prognostic factors such as good performance status (PS) and immunologic function, can obtain a high complete remission (CR) rate, either with low dose[1] or standard dose chemotherapy.[2] Despite these relatively high CR rates, a review of the literature indicates 35–55% of these patients ultimately die from the progression of their HIV-NHL.[1–8] In our experience of 105 patients with HIV-NHL at the Centro di Riferimento Oncologico in Aviano, Italy, 49% of patients did not achieve a CR, and 24% of patients who

obtained a CR after first-line chemotherapy ultimately relapsed. The median survival was 7 months and resistant or relapsed NHL was the primary cause of death in 44% of the patients. There is no consensus on the optimal approach to patients with HIV-NHL who fail first-line therapy; many physicians favor no chemotherapy at all, whereas others suggest palliative chemotherapy in selected patients. Moreover, there is very little experience reported in the literature on the feasibility and activity of second-line treatments in patients with relapsed or resistant HIV-NHL.[9-11] Based on these considerations, we performed a prospective study using a second-line combination chemotherapeutic regimen in this setting. This regimen was comprised of etoposide, mitoxantrone, and prednimustine, an ester of chlorambucil (47%) and prednisolone (53%). Etoposide, mitoxantrone, and prednimustine (VMP) is a regimen specifically devised and safely used at our institution in elderly (>70 years of age) patients with unfavorable NHL,[12] i.e., patients at high risk of chemotherapeutic side effects. VMP is actually composed of proven effective and relatively safe single agents and it is part of two active and safe regimens presently available for malignant lymphoma.[13,14]

PATIENTS AND METHODS

Twenty-one patients with resistant (13 patients) or relapsed (8 patients) HIV-NHL were treated from April 1992 and February 1995 at 5 different centers participating in the GICAT (Gruppo Italiano Cooperativo AIDS & Tumori, Italian Cooperative Group on AIDS and Tumors) activities. Resistant NHL was defined as progression or failure to obtain a CR with first-line chemotherapy, whereas relapsed NHL was defined as progression after CR of at least 1-month duration from the end of first-line chemotherapy. All patients were evaluated for extent of NHL before administration of VMP by physical examination, complete blood cell count, blood chemistry, chest radiographs, computerized tomography of the abdomen and brain, bone marrow aspirate and biopsy, and lumbar puncture for cerebrospinal fluid cytology.

Complete evaluation of all previously identified sites of disease was made to define response. No patients had evidence of active opportunistic infections. Only patients who received no more than one prior regimen of chemotherapy before VMP institution were eligible for this study. Informed consent was required from all patients before the start of therapy.

Etoposide and prednimustine were both given orally at doses of 80 mg/m^2 daily for 5 days, and mitoxantrone was given intravenously (i.v.) at a dose of 10 mg/m^2 on Day 1; all drug doses were repeated every 3 weeks. Chemotherapy was administered on an outpatient basis. When bone marrow toxicity was present, VMP was delayed on a weekly basis until bone marrow recovery. Therapy was repeated until the achievement of CR, disease progression, or toxicity. When CR was first documented, patients received two more cycles of chemotherapy. Granulocyte-colony stimulating factor (G-CSF) was given subcutaneously at a dose of 5 μg/kg/day beginning on Day 6 at the discretion of the treating physician to patients experiencing severe granulocytopenia, i.e., Grade 4 granulocytopenia in the previous cycle. Patients could receive any antiretroviral therapy that their physicians thought to be appropriate. All patients received *Pneumocystis carinii* pneumonia prophylaxis (160 mg trimethoprim/800 mg sulfamethoxazole once daily). Assessment of toxicity was performed according to the World Health Organization (WHO) criteria.[15] The criteria for response evaluation were as follows: CR was defined as the absence of all signs and symptoms of the disease for at least 1 month; PR as a reduction of more than 50% of all the measurable lesions for at least 1 month; and no response (NR) as less than a PR or increase in the area of the measurable disease or development of new lesions. Patients were evaluable for toxicity after 1 day of therapy, and evaluable for response after at least one cycle of therapy. Response duration was computed from the date of maximal response to the date of documented disease recurrence or progression. Survival was calculated from the day of the start of VMP treatment to death or to the last patient contact. Survival curves were estimated by the Kaplan–Meyer method.[16] Comparison of survival curves was performed using the log rank test.[17]

RESULTS

The clinical characteristics of the patients are listed in Table 1. The median PS according to the Eastern Cooperative Oncology Group (ECOG) was 2 (range, 0 to 3). Approximately one-half of the patients were former intravenous drug users, reflecting the epidemiology of HIV infection in Italy. All patients had either intermediate grade (24%) or high grade (76%) histology. The prior chemotherapy regimens that these patients received are listed in Table 1. All but one patient received chemotherapy regimens including doxorubicin or other antracyclines. The overall absolute CD4+ cell median count at the start of VMP treatment was 60/mm^3 (range, 3 to 538/mm^3). Interestingly, the CD4+ cell median count in patients with resistant NHL was 13/mm^3 (range, 3 to 538/mm^2); whereas the median count in patients with relapsed NHL was 108/mm^3 (range, 25 to 251/mm^3). As far as the response to first-line chemotherapy is concerned, the median duration of the 8 CRs was 8 months (range, 6 to 56 months) whereas the 3 PRs had a duration of 2, 3, and 9 months, respectively.

Of the 21 patients who entered the study, 2 were not assessable for response: 1 due to early death of an unknown cause and 1 due to toxic death after the first

TABLE 1
Characteristics of Patients (no. = 21)

Characteristic	No. (%)
Median age, yr. (range): 33 (24–55)	
Sex	
Male	16 (76)
Female	5 (24)
Risk	
IVDU	11 (52)
Homosexual	5 (24)
Heterosexual	5 (24)
ECOG performance status	
0	1 (5)
1	6 (29)
2	8 (38)
3	6 (29)
Histology (WF)	
Diffuse, large cell (G)	5 (24)
Large cell, immunoblastic (H)	8 (38)
Small noncleaved cell (J)	6 (25)
Miscellaneous	2 (9)
First-line therapy	
CHOP	4
LD-CHOP	2
CHVmP-VB	5
LD-CHVmP-VB	2
ACVBP	6
VCR-PDN	1
CIOD	1
Response to first-line therapy	
Complete remission	8 (38)
Partial remission	3 (14)
No response	10 (48)

IVDU: intravenous drug users; WF: working formulation; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; LD CHOP: low dose (50% reduced dose of cyclophosphamide and doxorubicin)-CHOP; CHVmP-VB: cyclophosphamide, doxorubicin, teniposide, prednisone-vincristine, bleomycin; LD-CHVmP-VB: low dose (50% reduced dose of cyclophosphamide and doxorubicin)-CHVmP-VB; ACVBP: doxorubicin, cyclophosphamide, vinblastine, bleomycin, and prednisone; VCR-PDN: vincristine-prednisone; CIOD: cyclophosphamide, idarubicin, vincristine, prednisone. ECOG: Eastern Cooperative Oncology Group;

cycle. The median number of cycles actually administered was 2 (range, 1 to 5 cycles). Although it was permitted, no patients received antiretroviral therapy during treatment with VMP. One patient received 3 cycles of chemotherapy at 75% of the planned dose, due to a persistent thrombocytopenia. One-week delays in chemotherapy cycles occurred six times in three patients. CR occurred in 5 of 19 patients (26%; exact 95% confidence interval, 9–51%). Only 1 CR, of 6 months' duration, occurred in 12 evaluable patients with resistant NHL, whereas 4 CRs of 5, 6, 7+, and 12+ months duration, respectively, occurred in 7 evaluable patients with relapsed NHL. We observed only two PRs: one in the relapsed patient group and one in the resistant patient group. Ten of 12 patients with NR belonged to the resistant group. Two patients, belonging to the group with resistant NHL, had central nervous system lymphomatous involvement at the start of VMP treatment. In particular, they had secondary meningeal localization. Both patients received intrathecal therapy with cytosine arabinoside (50 mg twice weekly) during treatment with the VMP regimen. They did poorly and died of progressive meningeal and systemic disease. The toxic effects of VMP consisted predominantly of myelosuppression. Of 45 cycles evaluable for toxicity, severe neutropenia ($< 500/\mu L$) occurred in 19 (42%) cycles. Twelve patients actually received G-CSF for secondary prophylaxis. Severe thrombocytopenia ($< 25{,}000/\mu L$) occurred in 6 (13%) cycles, with a toxic death due to sepsis in the setting of a severe neutropenia observed in a patient with resistant NHL during the first cycle. Only 3 of 21 (14%) treated patients required hospitalization due to febrile neutropenia. In two of these patients, a culture-confirmed bacterial infection diagnosis was made, but it was not the cause of VMP discontinuation. No patient developed major opportunistic infections during chemotherapy or in the month after completion of therapy. Most patients experienced hair loss, whereas nausea and vomiting were infrequent and mild. We did not observe cardiac toxicity. Overall median survival was 2 months (range, < 1–13 months). Median survival for the 14 patients who did not have a CR was 2 months, whereas that of the 5 patients with CR was 13 months. Although the number of patients was small enough to require cautious interpretation, there was a statistically significant difference ($P = 0.004$) in survival rates when the curves of patients with CR and those without CR were compared. The median survival in 8 patients with relapsed NHL (7 months, range, < 1–13 months) was statistically significantly longer than that in 13 patients with resistant NHL (2 months, range < 1–6 months) ($P = 0.007$).

Seventeen of 21 (81%) patients died with persistance of their NHL. Of the four surviving patients, three are without evidence of disease.

DISCUSSION

The overall median survival of patients who fail first-line chemotherapy for HIV-NHL ranges from 2 to 5 months, depending on the initial prognostic factors.[1,8] In patients with relapsed or resistant HIV-NHL, there are only three Phase I–II studies with single agents and no data on combination chemotherapy regimens reported in the literature. In a Phase I dose escalation study, Kahn et al.[9] treated nine patients with relapsed HIV-NHL with 2-chlorodeoxyadenosine, with only two PRs achieved, whereas Tulpule et al.[10] treated nine patients with refractory HIV-NHL with anti-B4 (CD19) monoclonal antibody

conjugated with ricin, which resulted in only one CR and one PR. Interestingly, the median survival from the start of this therapy was 6.6 months. Most recently, Levine et al.[11] employed mitoguazone in 31 heavily pretreated patients with relapsed or refractory HIV-NHL with 2 CRs and 5 PRs observed, making mitoguazone an interesting drug for the treatment of NHL.

In our study, it appears that patients with progression of their lymphoma after successful first-line therapy (i.e., relapsed patients) are able to obtain a second CR in the majority of cases with the VMP regimen. In fact, of 7 evaluable relapsed patients, 4 obtained a second CR lasting for a median time of 5 months, and one of these patients survived for 13 months. It is possible that the use of the same chemotherapy regimens employed in the first-line setting could have resulted in outcomes similar to those obtained with the VMP regimen. Other etoposide-based regimens have been studied in the front-line treatment of patients with HIV-NHL.[18–20] In particular, Sparano et al.[20] reported encouraging results with the infusional cyclophosphamide, doxorubicin, and etoposide regimen. However, the VMP regimen was chosen because it contained drugs not present in the first-line therapies.

The overall survival of relapsed patients, 7 months, is statistically significantly longer than the survival of patients with resistant HIV-NHL (i.e., 2 months). The latter group is in fact a very unfavorable group of patients in whom only experimental approaches should be tested.[21] As in the general population with NHL, second-line chemotherapy is usually associated with severe bone marrow toxicity. This was also true in our patients with resistant or relapsed HIV-NHL, but only one toxic death was observed due to sepsis in the setting of neutropenia. However, G-CSF was not systematically given as a prophylaxis for neutropenia. The advantage of the VMP regimen is that it is feasible to administer on an outpatient basis, a very important aspect to be considered in this setting, because it is less expensive and usually better tolerated.

In conclusion, although the overall prognosis of patients with resistant and relapsed HIV-NHL is very poor, an effective palliative approach with a combination of etoposide, mitoxantrone, and prednimustine can be offered in these situations. This regimen has an acceptable toxicity profile. Modifications can be made to decrease myelosuppression, such as reducing doses of VMP or administering G-CSF to all patients after each cycle to hasten recovery from neutropenia. In our study, in patients who relapsed after first-line chemotherapy, the majority achieved a second CR, with some patients surviving for several months.

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