Cancer Chemother Pharmacol (1983) 11: 191–195

Cancer Chemotherapy and Pharmacology

CCNU in combination chemotherapy for advanced histologically unfavorable non-Hodgkin's lymphoma

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Summary. *During a 3-year period 39 evaluable patients with stage III and IV non-Hodgkin's lymphomas and unfavorable histologies were treated with a unique chemotherapeutic regimen based on a modified CHOP combination to which was added the nitrosourea, CCNU. Complete response was observed in six of 15 (40%) patients with diffuse poorly differentiated lymphocytic lymphoma (DPDL), four of 11 (36%) with diffuse mixed histiocytic lymphocytic (DML), and seven of 13 (54%) with diffuse histiocytic lymphoma (DHL). Of the 17 patients who achieved complete response, nine (53%) have remained continuously disease-free for > 2.5 years (2.7–4.1 years) from the onset of therapy: four of six with DPDL, two of four with DML, and three of seven with DHL. Median survival was 18.9 months for all patients, 18.9 months for those with DPDL, 17.4 months for those with DML, and 9.7 months for those with DHL. The median survival has not been reached for patients who attained a complete response, and will exceed 3.3 years. Central nervous system relapse was observed in three patients. In general, toxicity was moderate and consisted primarily of leukopenia, nausea, vomiting, and neurotoxicity. There were no drug-related deaths. The addition of CCNU to a modified CHOP combination resulted in an effective, generally well-tolerated out-patient regimen. However, it did not appear to decrease the rate of CNS relapse or improve current treatment results observed with other adriamycin-containing regimens for similar patients.*

Introduction

The nitrosoureas are alkylating agents and have been found to have antitumor activity in a number of malignancies, including lung cancer, colon cancer, multiple myeloma, and lymphoma [2]. Early clinical trials demonstrated single-agent activity of the nitrosoureas (18%–28%) in the treatment of non-Hodgkin's lymphomas without any appreciable differences between CCNU [1,(2-chloroethyl)-3-cycloethyl-1-nitrosourea], BCNU [1,3-bis(2-chloroethyl)-2-nitrosourea], and methyl-CCNU [1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea] [15]. In the treatment of Hodgkin's disease, however, CCNU was significantly superior to BCNU and methyl-CCNU [15]. These data led to the development of an effective alternative treatment program for advanced Hodgkin's disease, in which CCNU was substituted for nitrogen mustard in the MOPP regimen [3].

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Because of their lipid solubility, the nitrosoureas have undergone extensive evaluation in patients with primary brain tumors [15]; concentrations of CCNU in the cerebrospinal fluid approximated 50% of serum levels following oral doses of 30–100 mg/m^2 in man [6, 14]. In early 1976, Bunn et al. reported the propensity for central nervous system involvement by non-Hodgkin's lymphomas primarily of the diffuse histiocytic and undifferentiated types [1]. Administration of CCNU as a single dose at the initiation of cyclophosphamide treatment for Burkitt's lymphoma was found to significantly delay the onset of meningeal metastases [12].

These data suggested the addition of CCNU to a multidrug chemotherapeutic regimen for the treatment of advanced, unfavorable histologic varieties of non-Hodgkin's lymphomas. A unique five-drug regimen was designed, in which CCNU was added to the highly active combination of McKelvey et al. [13], which consisted of cyclophosphamide, adriamycin, vincristine, and prednisone.

Materials and methods

Subjects. During the period from September 1976 to October 1979 a prospective therapeutic trial was conducted in 54 patients with stage III and IV (Ann Arbor system) histologically unfavorable non-Hodgkin's lymphomas. Unfavorable histological types (Rappaport classification) included the following: diffuse poorly differentiated lymphocytic lymphoma (DPDL), diffuse mixed histiocytic lymphocytic lymphoma (DML), and diffuse histocytic lymphoma (DHL). Additional entry requirements included a leukocyte count of 4,000/mm^3 or greater, platelet count of 100,000/mm^3 or greater, presence of measurable disease to be used as an indicator of response, and written informed consent. Patients were excluded from study if there was a history of prior exposure to CCNU or adriamycin, but could have received cyclophosphamide, vincristine, prednisone, or other chemotherapeutic agents. There were 39 patients evaluable for analysis. Of the 15 inevaluable patients, six were found to have nodular lymphomas, two never received CCNU, and two had diagnoses other than lymphoma. The following factors excluded one patient each: improper stage (stage II), prior adriamycin, no measurable disease, suicide after one course, and refusal of treatment.

Pretreatment patient characteristics are given in Table 1. Prior chemotherapy (per number of patients) included the following: cyclophosphamide (5), vincristine (7), prednisone (6), nitrogen mustard (2), procarbazine (1), streptonigrin (1), and chlorambucil (1). Of the eight patients who had received

prior chemotherapy, one had received prednisone without other agents.

Performance status was defined as follows: 0, fully active without symptoms; 1, ambulatory with symptoms; 2, bedridden < 50% of the time; 3, bedridden > 50% of the time but capable of self-care; 4, bedridden 100% of the time and incapable of self-care.

Table 1. Patient characteristics

	Number	Percentage (%)
No. of patients	39	(100)
Median age (range)	61	(16–72)
No. of patients > 50 years	30	(77)
Race (white)	33	(85)
Sex (male)	21	(54)
Performance status		
0	10	(26)
1	22	(56)
2	6	(15)
3	1	(3)
Stage		
III	16	(41)
IV	23	(59)
Symptoms[a]		
A	23	(59)
B	16	(41)
Prior chemotherapy	8	(21)
Prior irradiation	9	(23)
Histology		
DPDL	15	(39)
DML	11	(28)
DHL	13	(33)

[a] A, no symptoms; B, symptoms, including night sweats or fever, or reduction of > 10% in body weight

Treatment design. Chemotherapy consisted of cyclophosphamide, 500 mg/m^2, IV, on day 1; adriamycin, 30 mg/m^2, IV, on day 1; vincristine, 1 mg/m^2, IV, on day 1; and prednisone, 40 mg/m^2, PO, on days 1 through 5. Treatment cycles were repeated every 3 weeks. Additionally CCNU, 50 mg/m^2, PO, was given on day 1 of every other treatment cycle (i.e., every 6 weeks). Dosage was modified according to pretreatment white blood cells and platelet counts. Maintenance chemotherapy consisting of cyclophosphamide, 500 mg/m^2, IV, every 3 weeks and CCNU, 80 mg/m^2, PO, every 6 weeks was given after a cumulative adriamycin dosage of 450 mg/m^2 to patients in complete or partial remission, and was continued for a maximum of 2 years. Early in the trial 13 patients were randomized to receive intradermal injections of MER, the methanol extraction residue of BCG. Because of lack of enthusiasm for the use of MER, perhaps owing to its cutaneous toxicity [9], the randomization was stopped in August 1978 and the trial was continued as a single-arm study. No significant differences in response or survival were noted between patients who received MER compared with those who did not between September 1976 and August 1978, and they were therefore included in the overall analysis of this study.

Evaluation of response. A complete response (CR) was a 100% reduction of all demonstrable tumor and no new area of malignancy. Verification of CR in patients with a previously positive bone marrow required a repeat bone marrow examination. A partial response (PR) was indicated by a 50% or greater reduction of the product of the longest perpendicular diameters of indicator lesions since first measured and no new area of malignancy. Repeat scans or bone marrow examination were not required in patients attaining a PR on the basis of physical examination or a simple test such as chest X-ray. Duration of response was calculated from the day an objective response was first noted.

Histology	Complete response (CR)		Partial response (PR)		CR + PR		Progression	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
All types (n = 39)	17	(44)	14	(36)	31	(79)	8	(21)
DPDL (n = 15)	6	(40)	5	(33)	11	(73)	4	(27)
DML (n = 11)	4	(36)	6	(55)	10	(91)	1	(9)
DHL (n = 13)	7	(54)	3	(23)	10	(77)	3	(23)

Table 3. Duration of response and survival[a]

Histology	Complete response		Partial response		Progression (survival)	All patients (survival)
	Duration	Survival	Duration	Survival		
All types (n = 39)	> 23.8 (2.2–43.3)	> 39.9 (3.0–51.9)	4.0 (1.1–43.4+)	15.8 (5.8–70.3+)	3.3 (0.1–52.2)	18.9 (0.1–70.3+)
DPDL (n = 15)	> 24.2 (12.4–44.0+)	> 33.9 (16.4–48.0+)	15.6 (1.2–30.1)	28.1 (9.7–70.3+)	3.3 (0.1–12.1)	18.9 (0.1–70.3+)
DML (n = 11)	> 14.6 (2.2–22.7+)	> 45.8 (3.0–47.1+)	4.6 (2.7–43.4+)	21.4 (5.8–46.8+)	–[b]	17.4 (3.0–52.2)
DHL (n = 13)	> 36.3 (4.0–43.3)	> 43.9 (7.7–51.9)	1.4 (1.1–4.4)	7.1 (6.0–12.8)	1.8 (1.8–4.7)	9.7 (1.8–51.9)

[a] Median duration of response and survival in months (range)

[b] Only one patient with DML failed to respond to the treatment regimen (survival = 52.2 months)

Results

Response and survival

Objective responses (CR + PR) were observed in 79% of the patients (Table 2). Complete responses occurred in 40% of patients with DPDL, 36% of patients with DML, and 54% of patients with DHL, giving an overall CR rate of 44%.

The median duration of CR for the overall group has not been reached (Table 3) and will exceed 23.8 months, varying from 14.6+ months for DML through 24.2+ months for DPDL to 36.3+ months for DHL. The median duration of PR for the overall group of patients was 4.0 months, and varied from 1.4 months for DHL to 15.6 months for DPDL. Of the eight patients who had received prior chemotherapy, five achieved an objective response, including two CRs (duration, 37.1+ and 44.0+ months).

The median survival for the entire group of patients was 18.9 months (Table 3). Survivorship was directly dependent upon the degree of responsiveness to the treatment regimen (Table 3 and Fig. 1). The median survival in patients whose maximal response was progressive disease (PD), PR, and CR was 3.3, 15.8, and > 39.9 months, respectively ($P < 0.0001$; Breslow-Wilcoxon). Of the 17 patients who attained CR, five have died of progressive disease; one patient died of a second malignancy with no evidence of lymphoma at autopsy. All the patients without an objective response and all but three of the 14 patients with PR have died. The median survival of patients achieving CR has not been reached and will exceed 33.9, 45.8, and 43.9 months for patients with DPDL, DML, and DHL, respectively. Progression-free survival is depicted in Fig. 2.

Of the 17 patients who attained CR (Table 4), nine (53%) remain disease-free: four of six with DPDL; two of four with DML; and three of seven with DHL. With respect to the total number of patients, nine of 39 (23%) remain disease-free: four of 15 (27%) with DPDL; two of 11 (18%) with DML, and four of 13 (31%) with DHL. Maintenance therapy was given to 10 patients (7 CR, 3 PR) for one to 18 courses (median 9); of these patients six remain disease-free.

The CNS (meningeal lymphoma) was the initial site of relapse in three patients with CR (1 with DHL and 2 with DPDL), one of whom had concomitant relapse in the skin (Table 4). Relapse was not observed in the central nervous system of patients whose maximal response was PR.

In an attempt to identify certain factors that might be associated with the ability to attain CR, the strength of association between pretreatment characteristics (Table 1) and CR was tested independently. Performance status appears to be the only significant variable. All the 17 patients who attained CR had a performance status of 0–1, whereas only 15 of 22 patients (68%) failing to achieve CR had this level of performance ($P = 0.01$; Fisher's exact test). A stepwise logistic regression model was then used to determine which variables jointly were significantly associated with CR. Only performance status was found to be significantly associated with CR at the 0.1 level. No other variables (of the ones listed in Table 1), adjusted for performance status, were significantly associated with CR. Additionally, increased myelosuppression (moderately severe to severe) was not associated with an increased likelihood of complete response.

Toxicity

In general, toxicity was moderate. Hematologic toxicity of a severe or moderately severe degree was observed in 10 patients (26%), and consisted primarily in transient leukopenia (Ta-

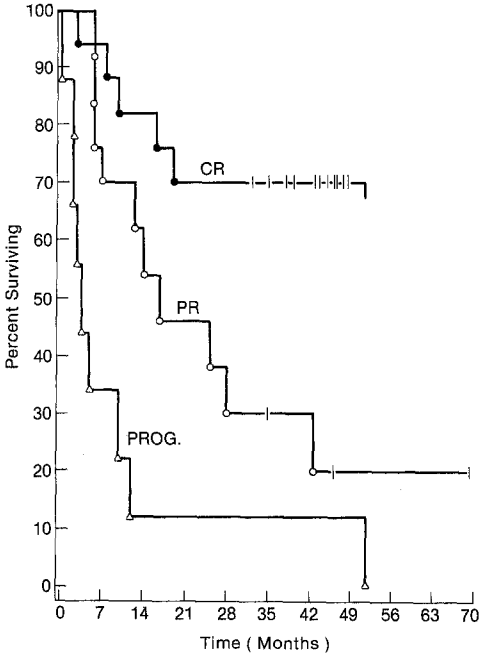

Fig. 1. Survival of patients with advanced histologically unfavorable non-Hodgkin's lymphomas following treatment with CCNU, cyclophosphamide, adriamycin, vincristine, and prednisone. Median survival times from the onset of therapy according to maximal response are > 39.9 months for complete response (●———●), 15.8 months for partial response (○———○), and 3.3 months for progression (△———△); $P < 0.0001$ (Breslow-Wilcoxon)

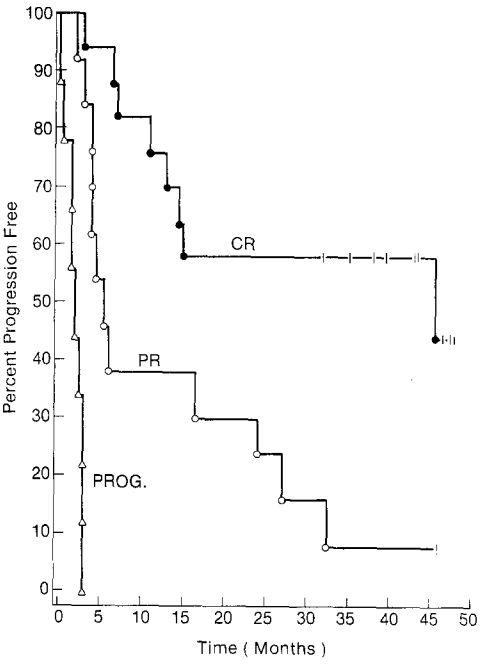

Fig. 2. Progression-free survival of patients with advanced histologically unfavorable non-Hodgkin's lymphomas following treatment with CCNU, cyclophosphamide, adriamycin, vincristine, and prednisone. Median times to progression from the onset of therapy according to maximal response are > 35.0 months for complete response (●———●), 5.3 months for partial response (○———○), and 1.8 months for progression (△———△); $P < 0.0001$ (Breslow-Wilcoxon)

Table 4. Characteristics, duration of response, and survival of patients with a complete response

Patient	Age (years)	Sex	Histology	Initial disease sites	Duration of response (months)	Sites of relapse	Survival (months)
J. G.	67	M	DPDL	Skin, nasopharynx, CSF	12.4	CSF, skin	18.9
N. H.	55	F	DPDL	Nodes	13.2	CSF	16.4
R. C.	71	F	DPDL	Nodes	23.8 +	–	35.4 +
C. S.	45	M	DPDL	Nodes	24.6 +	–	39.9 +
T. F.	22	M	DPDL	Nodes	30.2 +	–	32.4 +
P. P.	61	F	DPDL	Nodes, spleen, marrow	44.0 +	–	48.0 +
L. S.[a]	62	F	DML	Nodes	2.2	–	3.0
R. F.	58	F	DML	Nodes	6.5	Nodes	47.1 +
S. B.	60	F	DML	Nodes, marrow, skin, rectum, false vocal cord	22.7 +	–	44.6 +
B. J.	63	F	DML	Nodes	40.4 +	–	46.9 +
J. B.	71	F	DHL	Nodes, colon, ileum, liver, marrow	4.0	CSF	7.7
K. K.	16	F	DHL	Nodes, breast, pleural effusion, ascites	5.1	Nodes, breast	9.7
W. H.	70	M	DHL	Nodes, pleural effusion, lung, subcutaneous mass	14.0	Nodes, pleural effusion, lung	45.5 +
L. B.	61	M	DHL	Nodes	36.3 +	–	48.6 +
E. K.	61	M	DHL	Nodes	37.1 +	–	38.9 +
E. N.	54	M	DHL	Nodes, stomach	40.4 +	–	43.9 +
R. C.	63	F	DHL	Nodes	43.3	Nodes	51.9

[a] Patient died of a second malignancy (carcinoma of the gallbladder) with no evidence of lymphoma at autopsy

Table 5. Maximum hematologic toxicity

WBC			Platelets			Hemoglobin		
$\times 10^3/mm^3$	No. of patients (%)		$10^3/mm^3$	No. of patients (%)		g%	No. of patients (%)	
> 4,000	5	(13)	> 150	20	(51)	> 12	12	(31)
3,000–4,000	12	(32)	100–150	11	(28)	10–12	15	(38)
2,000–3,000	11	(28)	50–100	4	(10)	9–10	4	(10)
1,000–2,000	10	(26)	20–50	2	(5)	7–9	8	(21)
< 1,000	1	(3)	< 20	2	(5)	< 7	0	(0)

ble 5). There were four patients in whom leukopenia-related sepsis occurred, but none died. Thrombocytopenia < 50,000/mm^3 occurred in two patients, both of whom were given platelet transfusions and both of whom had bone marrow involvement with lymphoma.

Nonhematologic toxicity consisted primarily of effects on the gastrointestinal and neurologic systems. Nausea and vomiting were reported in 18 patients (46%). Neurotoxicity was observed in 18 patients (46%) and was less than grade 3 in all but one patient, who developed foot-drop. Mucositis was reported in four patients (10%). Cardiotoxicity was not observed and there were no drug-related deaths.

Discussion

The rate of complete response (44%) in the current trial is within the range of previously reported complete response rates (39%–81%) in patients with advanced unfavorable histologic types of non-Hodgkin's lymphomas treated with a variety of multidrug adriamycin-containing chemotherapeutic regimens [5]. Many of these responses in this trial have been durable. Nine of the 10 patients who were in complete remission for more than 2.5 years remain disease-free with a median follow-up of 3.7 years. Although differences in follow-up time make comparison difficult, these data do not represent an improvement in most of the previously reported multidrug programs, and in some cases suggest that this combination is not as effective as those used earlier [5].

The CHOP program (cyclophosphamide, adriamycin, vincristine, and prednisone) reported by McKelvey et al. resulted in CR rates of 68%, 87%, and 62% in stage III and IV DPDL, DML, and DHL, respectively [13]. Perhaps the lower CR rate in the current trial than in McKelvey's investigation is connected with the reduced dose levels of both cyclophosphamide and adriamycin, which were instituted to compensate for the additive myelosuppression expected with the addition of CCNU. However, the data of Elias et al., who treated patients with DHL with CHOP, appear somewhat similar to our own despite use of the same doses and schedule as were used by McKelvey et al.; the CR rate was 39% and approximately 30% of the patients were disease-free at 2 years [4]. Therefore, factors other than drug dosage, such as patient selection, might explain the differences among these studies.

During the current trial CNS relapse occurred in three patients (7.7%), one of whom had bone marrow involvement

at diagnosis; this was the primary site of relapse in two patients. Involvement of the CNS in the non-Hodgkin's lymphomas has been reported to occur in 5%–29% of the diffuse histologic varieties either at diagnosis or some time during the course of the disease [5, 7, 11, 16]. Although one cannot make a conclusive statement without a randomized trial, the addition of CCNU in the current trial does not appear to have appreciably reduced the incidence of lymphomatous involvement of the CNS. Similarly, CCNU was not effective in reducing the frequency of relapse in the CNS of patients with acute lymphoblastic leukemia [10] or small cell carcinoma of the lung [8].

In summary, the addition of the nitrosourea CCNU to a combination of cyclophosphamide, adriamycin, vincristine, and prednisone resulted in an effective well-tolerated out-patient regimen for the treatment of advanced non-Hodgkin's lymphomas of the unfavorable histological type. However, this unique combination appeared to be no more efficacious than other previously reported four- or five-drug regimens containing adriamycin. Also, the addition of this agent, which is known to penetrate the blood-brain barrier, did not appear to reduce the expected incidence of meningeal disease.

Acknowledgements. The authors thank the following members of the Piedmont Oncology Association for their patient contributions (number of patients contributed): Dr. W. Black, Salisbury, NC (1); Dr. R. Christian, Greenwood, SC (8); Dr. H. Goodwin, Charlotte, NC (1); Dr. R. Harding, Rutherfordton, NC (1); Dr. J. McCulloch, Spartanburg, SC (2); Dr. W. Porter, Charlotte, NC (1); Dr. W. Ramseur, Greenwood, SC (1). The support of the members of the Oncology Research Center – Piedmont Oncology Association statistical unit and the assistance with manuscript preparation by Denise James are acknowledged with appreciation.

This work was supported in part by CA12197 and CA33499 from the National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

References

1. Bunn PA Jr, Schein PS, Banks PM, Devita T Jr (1976) Central nervous system complications in patients with diffuse histiocytic and undifferentiated lymphoma: Leukemia revisited. Blood 47: 3–10
2. Colvin M (1982) The alkylating agents. In: Chabner B (ed) Pharmacologic principles of cancer treatment. Saunders, Philadelphia, pp 276–308
3. Cooper MR, Pajak TF, Nissen NII, Stutzman L, Brunner K, Cuttner JR, Falkson G, Grunwald H, Bank A, Leone L, Seligman BR, Silver RT, Weiss RB, Haurani F, Blom J, Spurr CL, Glidewell OJ, Gottlieb AJ, Holland JR (1980) A new effective four-drug combination of CCNU (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea) (NSC-79038), vinblastine, prednisone, and procarbazine for the treatment of advanced Hodgkin's disease. Cancer 46: 654–662
4. Elias L, Portlock CS, Rosenberg SA (1978) Combination chemotherapy of diffuse histiocytic lymphoma with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP). Cancer 42: 1705–1710
5. Glick JH (1981) Chemotherapy of Hodgkin's and non-Hodgkin's lymphomas. In: Bennett JM (ed) Lymphomas 1 including Hodgkin's disease. Martinus Nijhoff, Boston, pp 343–446
6. Hansen HH, Selawry OS, Muggia FM, Walker MD (1971) Clinical studies with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC-79037). Cancer Res 31: 223–227
7. Herman TS, Hammond N, Jones SE, Butler JJ, Byrne GE Jr, McKelvey EM (1979) Involvement of the central nervous system by non-Hodgkin's lymphoma. Cancer 43: 390–397
8. Jackson DV Jr, Richards F II, Cooper MR, Ferree C, Muss HB, White DR, Spurr CL (1977) Prophylactic cranial irradiation in small cell carcinoma of the lung. JAMA 237: 2730–2733
9. Jackson DV Jr, Paschal BR, Ferree C, Richards F II, Muss HB, Cooper MR, White DR, Stuart JJ, Spurr CL, Wells B, Sartiano G, McFarland J, McCulloch J (1982) Combination chemotherapy-radiotherapy with and without the methanol-extraction residue of bacillus Calmette-Guérin (MER) in small cell carcinoma of the lung. Cancer 50: 48–52
10. Kung FH, Nyhan WL, Cuttner J, Falkson G, Lanzkowsky P, Del Duca V, Nawabi IU, Koch K, Pleuess H, Freeman A, Burgert EO, Leone LA, Ruymann F, Patterson RB, Degnan T, Hakami N, Pajak TF, Holland J (1978) Vincristine, prednisone, and L-asparaginase in the induction of remission in children with acute lymphoblastic leukemia following relapse. Cancer 41: 428–434
11. Levitt LJ, Dawson DM, Rosenthal DS, Moloney WC (1980) CNS involvement in the non-Hodgkin's lymphomas. Cancer 45: 545–552
12. Magrath IT, Ziegler JL (1973) Prophylaxis of meningeal Burkitt's lymphoma with CCNU. Proc Am Assoc Cancer Res 14: 67
13. McKelvey EM, Gottlieb JA, Wilson HE, et al. (1976) Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer 38: 1484–1493
14. Oliverio VT, Walker MD, Hayes SL, Devita VT (1970) The physiologic distribution of radioactive 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) in man. Proc Am Assoc Cancer Res 11: 61
15. Wasserman TH, Slavik M, Carter SK (1975) Clinical comparison of the nitrosoureas. Cancer 36: 1258–1268
16. Young RC, Howser DM, Anderson T, Fisher RI, Jaffe E, DeVita VT (1979) Central nervous system complications of non-Hodgkin's lymphoma. Am J Med 66: 435–443

Received February 17, 1983/Accepted July 21, 1983