Acta Medica Okayama

Volume 36, *Issue* 1 1982 *Article* 7

FEBRUARY 1982

Combination chemotherapy of advanced non-Hodgkin's lymphoma with adriamycin, vincristine, ifosfamide and prednisolone (AVIP): a preliminary report

Taisuke Ohnoshi, *Okayama University*
Akira Oka, *Okayama University*
Kyoichi Hayashi, *Okayama University*
Hiroshi Ueoka, *Okayama University*
Masaharu Sato, *Okayama University*
Ryuji Nishihara, *Okayama University*
Masatoshi Yasuoka, *Okayama University*
Yasuhiro Sando, *Okayama University*
Toshio Tanaka, *Okayama University*
Ikuro Kimura, *Okayama University*

Combination chemotherapy of advanced non-Hodgkin's lymphoma with adriamycin, vincristine, ifosfamide and prednisolone (AVIP): a preliminary report*

Taisuke Ohnoshi, Akira Oka, Kyoichi Hayashi, Hiroshi Ueoka, Masaharu Sato, Ryuji Nishihara, Masatoshi Yasuoka, Yasuhiro Sando, Toshio Tanaka, and Ikuro Kimura

Abstract

Eighteen patients with advanced non-Hodgkin's lymphoma other than the diffuse histiocytic type were treated with a combination of adriamycin, vincristine, ifosfamide and prednisolone (AVIP). The objective response rate was 83% (15/18); 61% (11/18) achieved complete remission. The median duration of complete remission was 11 months ranging from 2 to 39+ months. Eleven of the 18 patients are still alive during the median follow-up time of 13 months. The median survival was 14+ months for complete responders, and 9.5 months for partial and nonresponders. A myelosuppressive toxicity was well tolerated. AVIP offers some hope as treatment of advanced non-Hodgkin's lymphoma.

KEYWORDS: non-Hodgkin's lymphoma, combination chemotherapy

---

*PMID: 7064735 [PubMed - indexed for MEDLINE]

Acta Med. Okayama 36, (1), 67—72 (1982)

COMBINATION CHEMOTHERAPY OF ADVANCED NON-HODGKIN'S LYMPHOMA WITH ADRIAMYCIN, VINCRISTINE, IFOSFAMIDE AND PREDNISOLONE (AVIP): A PRELIMINARY REPORT

Taisuke OHNOSHI, Akira OKA, Kyoichi HAYASHI, Hiroshi UEOKA, Masaharu SATO, Ryuji NISHIHARA, Masatoshi YASUOKA, Yasuhiro SANDO, Toshio TANAKA* and Ikuro KIMURA

*Second Department of Medicine; and * Pathology Section, Central Laboratories, Okayama University Hospital, Okayama 700, Japan*

Received August 26, 1981

Abstract. Eighteen patients with advanced non-Hodgkin's lymphoma other than the diffuse histiocytic type were treated with a combination of adriamycin, vincristine, ifosfamide and prednisolone (AVIP). The objective response rate was 83 % (15/18); 61 % (11/18) achieved complete remission. The median duration of complete remission was 11 months ranging from 2 to 39+ months. Eleven of the 18 patients are still alive during the median follow-up time of 13 months. The median survival was 14+ months for complete responders, and 9.5 months for partial and nonresponders. A myelosuppressive toxicity was well tolerated. AVIP offers some hope as treatment of advanced non-Hodgkin's lymphoma.

Key words : non-Hodgkin's lymphoma, combination chemotherapy.

Several studies have shown that combination chemotherapy is superior to single-drug therapy in the treatment of non-Hodgkin's lymphoma (NHL) (1, 2). However, even with the introduction of COP or CVP (combination of cyclophosphamide, vincristine and prednisolone), complete remission has been infrequent and the overall survival is poor (1-3). Recently, combinations including new active agents such as adriamycin and bleomycin have been introduced; these appear to produce long-term remission in a substantital proportion of patients with advanced NHL (4, 5).

Ifosfamide (IF) is a derivative of cyclophosphamide (CPA) which is effective against a CPA-resistant L1210 leukemia (6). In a clinical trial, this agent proved to be effective for NHL which had been resistant to CPA therapy (7). A combination of four drugs consisting of adriamycin (ADM), vincristine (VCR), ifosfamide (IF) and prednisolone (PS) (AVIP) was initiated in 1975 for treatment of the patients with advanced NHL who had received prior chemotherapy, and the results were reported in 1980 (8). On the basis of the effectiveness of AVIP demonstrated in our study, AVIP was introduced as first choice combina-

tion chemotherapy for previously untreated NHL patients other than those with diffuse histiocytic lymphoma (DH). The preliminary results of AVIP are reported in this communication. Patients with DH were given BCOP (combination of bleomycin, CPA, VCR and PS) which was rather more effective than AVIP because there was less myelosuppressive toxicity (9).

MATERIALS AND METHODS

The present study consists of 18 patients with advanced NHL other than DH. All the original sections were reviewed and classified according to the histopathologic criteria of Rappaport (10). The procedures for determination of clinical staging included chest roentgenography, upper abdominal computerized tomography, bone survey and scan, bonc marrow biopsy and aspiration, and liver biopsy under peritoneoscopy. Bilateral pedal lymphography was performed only in the patients who did not have obvious stage IV disease. The extent of disease was categorized according to the Ann Arbor staging classification (11).

Chemotherapy consisted of a combination of ADM, VCR, IF and PS (AVIP). The dosage, route and schedule are listed in Table 1. According to the degree of myelosuppression observed in previous courses, the doses of ADM and IF were decreased by 25% to 50% in subsequent courses. ADM was administered up to 500 mg/m^2 of the body surface area, unless signs of cardiomyopathy were detected with ECG, myocardial scintigram using ^{99m}Tc-pyrophosphate or echocardiogram. Whenever disease progressed after two courses of AVIP, the therapy was discontinued and patients were treated with other therapies.

TABLE 1. AVIP REGIMEN*

Drug	Dose (mg/kg)	Route	Schedule
Adriamycin (ADM)	1.2	i.v.	Day 1
Vincristine (VCR)	0.03	i.v.	Day 1
Ifosfamide (IF)	50	i.v.	Day 1
Prednisolone (PS)	1	p.o.	Days 1-5

* Courses repeated three-weekly. i.v. : intravenous; p.o. : per oral.

Complete remission (CR) was defined as the disappearance of all "measurable disease" for a minimum of one month, and normalization of all laboratory and radiographic parameters that had been abnormal prior to therapy. A reduction of greater than 50% in the "measurable disease" which lasted for a minimum of one month or a complete disappearance of disease which recurred within one month was considered to be a partial remission (PR). Re-staging procedures including bone marrow biopsy and radiographic examinations were performed in all patients. The duration of remission was calculated from the time of the first evidence of CR or PR to relapse, and survival was calculated from the day of initiating AVIP.

RESULTS

Table 2 shows the clinical profile, response to chemotherapy, duration of

TABLE 2. PATIENTS' CLINICAL PROFILE AND MODE OF RESPONSE TO AVIP

Case number	Histology	Age	Sex	Stage	Extranodal involvement (s)	Response to AVIP	Response duration (Month)	Survival (Month)
1.	NPDL	51	M	IV	BM, bone	CR	39+	42+
2.	DPDL	27	M	IV	pleura	CR	6.5	28.5
3.	DPDL	45	M	III	(−)	CR	26+	27+
4.	NH	45	M	III	(−)	CR	11	19+
5.	DWDL	53	M	IV	BM	CR	14+	17+
6.	DPDL	56	M	III	(−)	CR	13+	14+
7.	DPDL	42	F	IV	BM, liver	CR	9.5+	11+
8.	DPDL	46	F	IV	liver	CR	7+	10+
9.	DPDL	65	M	IV	BM, liver, bone	CR	4	8.5
10.	DPDL	58	M	IV	BM	CR	2.5	7
11.	DM	52	F	III	(−)	CR	2	6+
12.	DWDL	41	M	IV	BM	PR	10+	12+
13.	NPDL	61	M	III	(−)	PR	9+	10+
14.	DWDL	65	M	IV	BM, skin, periph. blood	PR	4.5	9.5
15.	DPDL	48	F	III	(−)	PR	4	10
16.	DWDL	53	F	III	(−)	NR	(−)	13+
17.	DPDL	50	M	IV	liver, pleura	NR	(−)	5+
18.	DU	17	M	II	(−)	NR	(−)	4.5

NPDL : Nodular poorly diff. lymphocytic; DPDL : Diffuse poorly diff. lymphocytic; NH : Nodular histiocytic; DWDL : Diffuse well diff. lymphocytic; DM : Diffuse mixed lymphocytic and histiocytic; DU : Diffuse undiff. ; BM : Bone marrow; CR : Complete remission; PR : Partial remission; NR : Non-remission.

response and survival of 18 patients. The patients ranged from 17 to 65 years old (median: 51), and consisted of 13 males and 5 females. No patients had prior chemo- and/or radio-therapy. All the patients, except one (patients 18) with bulky abdominal masses, had advanced disease; 55 % of them were in stage IV. Extranodal spread of the disease was found in the bone marrow and liver in most of the patients.

Response rates according to the histologic classification are listed in Table 3. Eleven of 18 patients (61 %) achieved CR and the overall response rate, *i.e.*, CR plus PR, was 83 %. The CR rate of patients with favorable histologies (12), *i.e.*, nodular poorly differentiated lymphocytic (NPDL) and diffuse well differentiated lymphocytic (DWDL), was 33 %, while that of patients with unfavorable hisologies, *i.e.*, nodular histiocytic (NH), diffuse poorly differentiated lymphocytic (DPDL), diffuse mixed lymphocytic and histiocytic (DM) and diffuse undifferentiated (DU), was 75 %. The duration of response in two complete responders with favorable histologies was 42+ and 14+ months. Of nine complete responders with unfa-

TABLE 3. RESPONSE RATE TO AVIP ACCORDING TO HISTOLOGIC CLASSIFICATION

Histologic classification	No. of patients	CR	PR	NR	CR+PR
Nodular poorly diff. lymphocytic (NPDL)	2	1	1	0	2
Diffuse well diff. lymphocytic (DWDL)	4	1	2	1	3
Nodular histiocytic (NH)	1	1	0	0	1
Diffuse poorly diff. lymphocytic (DPDL)	9	7	1	1	8
Diffuse mixed lymphocytic and histiocytic (DM)	1	1	0	0	1
Diffuse undiff. (DU)	1	0	0	1	0
Total	18	11 (61%)	4	3	15 (83%)

CR : Complete remission; PR : Partial remission; NR : Non-remission.

vorable histologies, four patients relapsed after 2, 2.5, 4 and 6.5 months, of whom three discontinued the chemotherapy within three months. The remaining five have maintained CR for 6 to 39 months.

Eleven of the 18 patients are still alive during the follow-up time of between 6 and 42 months. Five of six patients with favorable histologies (Patients 1, 5, 12, 13, 14 and 16) are alive despite a poor CR rate (33 %) to AVIP. The median survival of the remaining 12 patients with unfavorable histologies was 10+ months ranging from 13+ months for complete responders to 5 months for partial and nonresponders.

The major complications during chemotherapy with AVIP were myelosuppression and alopecia. Alopecia developed in all patients, while myelosuppression occurred in most patients (72 %); the latter varied depending on the bone marrow reserve of the patients and on the dosage given. The highest myelosuppression occurred on day 14 of the course with a return to normal in most instances by three weeks, and no patients developed severe infection or hemorrhagic problems. Genitourinary toxicity due to IF developed in four patients; this consisted mainly of microscopic hematuria and a sense of irritation of the bladder, but the symptoms subsided within a few days after taking adequate quantities of water. Other side effects included upper gastrointestinal disturbance in 12 patients, peripheral neuropathy in 7, elevation of s-GOT in 6, and stomatitis in 2. Six patients did not develop cardiomyopathy in spite of receiving ADM at a cumulative total dose of 500 mg/m^2.

DISCUSSION

The objective of the present study was to increase the CR rate and thus

increase survival in patients with advanced NHL based on the fact that only patients who achieved CR had increased survival (1, 4, 5, 9).

The favorable prognosis of patients with a nodular pattern in their lymph nodes was recognized even in stage Ⅲ or Ⅳ. Jones *et al.* (12) identified four histologic types that were favorable in terms of response to treatment and survival: DWDL, NPDL, nodular mixed lymphocytic-histiocytic, and nodular well differentiated lymphocytic lymphomas. In our series of patients with favorable histologies, five of six patients are still alive although the CR rate of 33 % was not impressive compared to the rate obtained by COP or CVP regimens (1, 3, 13). The results suggest that intensive combination chemotherapy such as AVIP is still controversial for the treatment of NHL patients with favorable hisologies.

Therefore, the chemotherapy of patients with unfavorable histologies presents a difficult task. The 75 % CR rate in our series of patients with unfavorable histologies who were treated with AVIP appears to be an improvement over COP or CVP (1, 3, 13), and is comparable to the rate for intensive combination chemotherapy including ADM (4, 5, 14). Four of nine complete responders with unfavorable histologies relapsed within 6.5 months; the short duration of response might have been due to early discontinuation of chemotherapy. Nevertheless, the median survival of all the patients with unfavorable histologies was longer with AVIP than with COP (1, 13). Improved survival in complete responders compared to partial and non-responders supports the introduction of intensive chemotherapy employing ADM in the treatment of NHL patients with unfavorable histologies.

The significance of IF still remains to be determined, although the effectiveness of AVIP was evident and the degree of toxicity of AVIP was no higher than that reported previously with other combinations (4, 5, 14). This should be clarified through a control study comparing AVIP with a combination of CPA, ADM, VCR and PS (CHOP) (5); the last represents replacement of IF with CPA.

REFERENCES

1. Luce, J.K., Gamble, J.F., Wilson, H.E., Monto, R.W., Isaacs, B.L., Palmer, R.L., Coltman, C.A., Jr., Hewlett, J.S., Gehan, E.A. and Frei, E., Ⅲ : Combined cyclophosphamide, vincristine, and prednisone therapy of malignant lymphoma. *Cancer* **28,** 306-317, 1971.
2. DeVita, V.T., Jr., Young, R.C. and Canellos, G.P.: Combination versus single agent chemotherapy: A review of the basis for selection of drug treatment of cancer. *Cancer* **35,** 98-110, 1975.
3. Bagley, C., Jr., Berard, C. and Canellos, G.P.: Advanced lymphosarcoma, intensive cyclical combination chemotherapy with cyclophoaphamide, vincristine, and prednisone. *Ann. Intern. Med.* **76,** 227-234, 1972.
4. Skarin, A.T., Rosenthal, D.S., Moloney, W.C. and Frei, E., Ⅲ: Combination chemotherapy of advanced non-Hodgkin lymphoma with bleomycin, adriamycin, cyclophosphamide,

vincristine, and prednisone (BACOP). *Blood* **49,** 759-770, 1977.

5. Elias, L., Portlock, C.S. and Rosenberg, S.A.: Combination chemotherapy of diffuse histiocytic lymphoma with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP). *Cancer.* **42,** 1705-1710, 1978.
6. Brock, N.: Pharmacological study with ifosfamide- a new oxazaphosphorine compound (Proceedings of the 7th International Congress of Chemotherapy, Prague, 1971). In *Advances in Antimicrobial and Antineoplastic Chemotherapy,* ed. M. Semonsky, M. Hejzler and S. Masák, vol. 2, University Park Press, Baltimore, pp. 749-756, 1972.
7. Rodriguez, V., McCredie, K.B., Keating, M.J., Valdivieso, M., Bodey, G.P. and Freileich, E.J.: Isophosphamide therapy for hematologic malignancies in patients refractory to prior treatment. *Cancer Treat. Rep.* **62,** 493-497, 1978.
8. Kimura, I., Ohnoshi, T., Oka, A., Nakata, Y., Hayashi, K., Sato, M., Nishihara, R., Tanaka, T. and Sezaki, T.: Clinical efficacy of four-drug combination of adriamycin, vincristine, ifosfamide, and prednisolone for patients with malignant lymphoma, especially relapsed or refractory types. *Jpn. J. Clin. Hematol.* **21,** 785-791, 1980 (in Japanese).
9. Kimura, I., Ohnoshi, T., Nakata, Y., Hiraki, S., Urabe, Y., Fujii, M., Hayashi, K., Sato, M., Kataoka, M., Nishihara, R., Terao, S., Mito, T. and Tanaka, T.: Therapeutic effect of combined administration of four drugs, vincristine, bleomycin, cyclophosphamide and prednisolone for patients with malignant lymphoma. *Jpn. J. Clin. Hematol.* **21,** 792-800, 1980 (in Japanese).
10. Rappaport, H.: *Tumors of the Hematopoietic System.* Armed Forces Institute of Pathology, Washington, D.C., pp. 91-206, 1966.
11. Carbone, P.P., Kaplan, H.S., Musshoff, K., Smithers, D.W. and Tubiana, M.: Report of the committee on Hodgkin's disease staging classification. *Cancer Res.* **31,** 1860-1861, 1971.
12. Jones, S.E., Fucks, Z., Bull, M., Kadin, M.E., Dorfman, R.F., Kaplan, H.S., Rosenberg, S.A. and Kim, H.: Non-Hodgkin's lymphomas. IV. Clinicopathologic correlation in 405 cases. *Cancer* **31,** 806-823, 1973.
13. Portlock, C.S. and Rosenberg, S.A.: Combination chemotherapy with cyclophosphamide, vincristine, and prednisone in advanced non-Hodgkin's lymphomas. *Cancer* **37,** 1275-1282, 1976.
14. Rodriguez, V., Cabanillas, F., Burgess, M.A., McKelvey, E.M., Valdivieso, M.V., Bodey, G.P. and Freileich, E.J.: Combination chemotherapy ("CHOP-Bleo") in advanced (non-Hodgkin) malignant lymphoma. *Blood* **49,** 325-333, 1977.