Cancer Chemother Pharmacol (1985) 15: 268–271

Cancer Chemotherapy and Pharmacology

The effects of multiple combination chemotherapy with vincristine, cyclophosphamide (Endoxan), methotrexate, 5-fluorouracil, adriamycin and prednisolone (VEMFAH) for advanced breast cancer

Tetsuhito Kojima[1],*, Akira Hoshino[1], Kanji Ohara[1], Osamu Kamiya[1], Koichiro Nagata[1], Yoshinori Ito[1], Tomohiro Kinoshita, Isamu Sugiura[2], Mitsuaki Yamada[2], Haruo Sato[2], Eiichi Nagura[3], and Yoshikazu Dohke[4]

[1] Division of Cancer Chemotherapy, Department of Medicine, and
[2] Department of Surgery, Anjo Kosei Hospital, Anjo-shi, Aichi, 446, Japan
[3] First Department of Internal Medicine, Nagoya University, School of Medicine, Nagoya-shi, Aichi, 461, Japan
[4] Department of Radiology, Saint Hamamatsu Hospital, Hamamatsu-shi, Shizuoka, 430, Japan

Summary. Thirty-eight patients with advanced breast cancer were treated with the 'VEMFAH' multiple-drug combination chemotherapy, consisting of vincristine (V), cyclophosphamide (Endoxan; E), methotrexate (M), 5-fluorouracil (F), adriamycin (A), and prednisolone (H). Disease response was evaluated by the UICC criteria. Among the 35 evaluable cases, 4 complete responses (CR), 23 partial responses (PR), 2 cases of no change (NC), and 6 of progressive disease (PD) were observed. The response rate (CR+PR) was 77.1%. The median duration of response was 52 weeks (8–192 weeks) or 12 months. In 32 patients who received more than two courses of therapy the 50% survival time of responders was 27.0 months, which was significantly longer than the 10.3 months of nonresponders ($P<0.05$). Except for 2 patients who developed myocardial damage, the therapy was never terminated because of side effects. Cumulative cardiotoxicity was not apparent in this study. This multiple-drug combination chemotherapy with 'VEMFAH' is concluded to be an effective treatment for advanced and disseminated breast cancer.

Introduction

Since the studies reported by Greenspan's group [12, 13] on combination chemotherapy with various anticancer drugs, there has been remarkable progress with regard to chemotherapy for advanced breast cancer during recent years.

Particular importance attaches to the regimen tested by Cooper (CMFVP) [8] in 1969, in which vincristine, cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone were used; the results documented a high response rate of 88%. Since then, several studies, in some of which various administration schedules of the above drugs have been used, have been conducted at various institutions and by cooperative study groups in the United States, with a reported response rate of 48.8% (out of 623 cases) [2].

The anthracycline antibiotic adriamycin, which was discovered by Arcamone [1] and DiMarco [10], has also been reported to have an excellent response rate of 40% (out of 881 cases) when used as a single agent [4]. The response rates when it was used in combinations were 56% [4] for adriamycin, 5-fluorouracil, and cyclophosphamide (FAC); 72% [20] for adriamycin, cyclophosphamide, and vincristine (VAC); and 62% [9] for adriamycin, cyclophosphamide, methotrexate, and 5-fluorouracil (CAMF). Adriamycin is currently considered the most effective single agent against breast cancer.

In our study, patients with recurrent advanced breast cancer were treated with the intensive and intermittent combination chemotherapy named VEMFAH [17], consisting of vincristine (V), cyclophosphamide (Endoxan; E), methotrexate (M), 5-fluorouracil (F), adriamycin (A), and prednisolone (H). This report documents the results of VEMFAH chemotherapy with reference to anticancer activities and side effects.

Patients and methods

A total of 38 patients with advanced breast cancer entered this study. All the patients had recurrence and metastasis of breast cancer after previous surgery for removal of ei-

Table 1. Patient characteristics

Age	No. of patients
30–39	5
40–49	14 (median 49)
50–59	15
60–69	4
Performance status (%)	
100–80	16
70–40	14
30– 0	8 (21.1%)
Prior treatments	
Chemotherapy	11
^{60}Co irradiation	5
^{60}Co + chemotherapy	15
Hormone therapy	7
None	6
Metastatic lesions	
Local and lymph nodes	21
Bone	21
Lung	6
Liver	5
Brain	4
Others	14
No. of metastatic lesions	
3 ≦	9
2	14
1	15

* *Present address:* Department of Internal Medicine, Saga Medical School, Saga, 840-01, Japan
Offprint requests to: A. Hoshino

ther one or both breasts. The metastatic lesions of each patient are recorded in Table 1, and 9 of the 38 patients had more than three metastatic lesions.

The characteristics of the 38 patients are also shown in Table 1. The age of patients ranged from 35 to 66 (median 49) years. There were 8 cases (21.1%) with a critical performance status (Karnofsky) of $\leq 30\%$ in this study. In all, 31 of the 38 patients had previously undergone chemotherapy or ^{60}Co irradiation either in single or in combination therapy, and 19 of 26 patients who had received prior chemotherapy received the chemotherapy for recurrent disease. There were only 2 cases in whom adriamycin had been used in the prior treatment; 30 mg and 40 mg, respectively, administered in to the thoracic cavity and in to the hepatic artery. In 7 cases hormone therapy had been given but the disease was resistant or the therapy was not effective.

The dose and schedule of VEMFAH combination therapy are shown in Fig. 1. and are as follows: vincristine 0.7 mg/m^2 by IV push on days 1, 8, 15, and 22; cyclophosphamide 333 mg/m^2 by IV infusion on day 1; methotrexate 13 mg/m^2 by IV push on day 1; 5-fluorouracil 333 mg/m^2 IV infusion daily for 5 days; adriamycin 40 mg/m^2 by IV bolus on day 1; prednisolone 60 mg/m^2 PO per day for 5 days with a gradual decrease of dose over 2 weeks. This regimen was repeated every 3 or 4 weeks, depending on recovery from bone marrow damage. Also, for patients who manifested severe bone marrow toxicity the doses of adriamycin, cyclophosphamide, and methotrexate were reduced 20%–25% from the second course on. In general, vincristine was administered once a week for the first course and was then given only on day 1 every 3 or 4 weeks. Furthermore, the dose of prednisolone was reduced if it caused occurrence of glucosuria and high blood sugar. Treatment was carried out until the total dose of adriamycin reached 500 mg/m^2 or it was necessary to terminate it due to toxicity.

Results

Assessment of the response to chemotherapy was based on the UICC program [14]. Three cases dropped out who had no evaluable lesion following surgery for total resection of the metastatic tumor. The remaining 35 cases from whose data Table 2 is made up showed a very high response rate of 77.1%. The data show 4 cases (11.4%) with complete response (CR), 23 cases (65.7%) with partial response (PR), 2 cases with no change (NC), and 6 cases with progressive disease (PD). As also shown in Table 2, the median response duration of responders (CR + PR) was 52 weeks (12 months). Of the 35 evaluable cases, 3 died during the first course of therapy, because of low performance status or heart failure. In the remaining 32 patients who received more than two courses of therapy, the 50% survival time was 27.0 months for the CR + PR group and 10.3 months for the NC + PD group according to the Kaplan-Meier method [18], (Fig. 2), and the performance status of nonresponders was as good as that of responders (PS in nonresponders: 100%–80% in 2 cases; 70%–40% in 2; and 30%–0% in 1; PS in responders; 100%–80% in 12; 70%–40% in 10; and 30–0% in 5). Thus, the prognosis of responders (CR + PR) was clearly much better than that of non responders (NC + PD) according to the generalized Wilcoxon test [11] ($P < 0.05$).

Table 2. Response of patients treated with VEMFAH

No. of patients entered	38
No. of patients evaluated	35
Complete response (CR)	4
Partial response (PR)	23 CR + PR = 77.1%
No change (NC)	2
Progresssive disease (PD)	6
Median duration of response	
CR + PR	52 weeks (12 months)
50% survival time[a]	
CR + PR	27.0 months
NC + PD	10.3 months

[a] In 32 patients who received more than two courses of the therapy

The number of treatments with VEMFAH ranged from 1 to 19 courses (mean 9.0 courses). The total amount of adriamycin used ranged from 27.4 to 648.0 (mean 330.5) mg/m^2. Seven patients received over 500 mg/m^2 adriamycin, but cardiotoxicity due to accumulation of the drug was not apparent. Rather, there were indications of resistance to VEMFAH therapy, and the study was terminated for this reason. Also, the median duration from the onset of therapy until PR was 11.6 weeks (mean 11.9 weeks), with the responsive cases manifesting responses almost from the

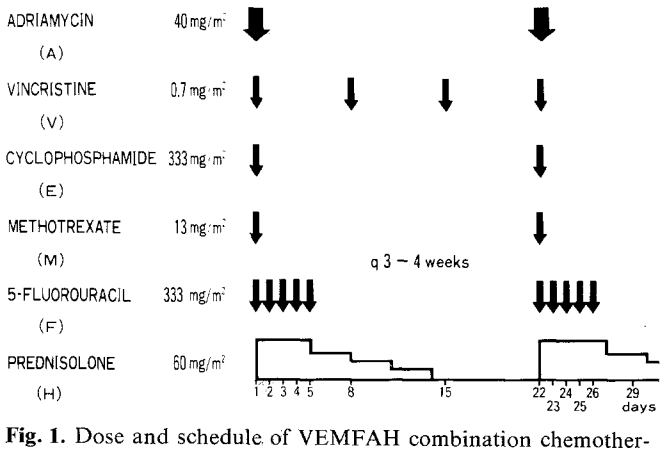

Fig. 1. Dose and schedule of VEMFAH combination chemotherapy

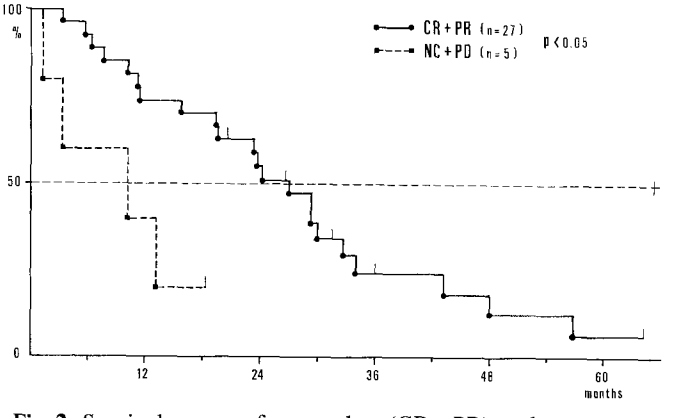

Fig. 2. Survival curves of responders (CR + PR) and nonresponder (NC + PD) among 32 patients treated with more than two courses of VEMFAH combination chemotherapy. The difference is statistically significant ($P < 0.05$)

Table 3. Side effects of VEMFAH therapy

Alopecia	34/34	100 %
Anorexia	19/37	51.4%
Nausea	15/37	40.5%
Vomiting	6/37	16.2%
Stomatitis	12/37	32.4%
Neuropathy	9/37	24.3%
Glucosuria	3/37	8.1%
sGOT, sGPT ↑	6/37	16.2%
ECG changes	14/37	37.8%
ST-T[a]	10/37	
VPC[a]	1/37	
Low voltage[a]	1/37	
Myocardial damage	2/37	5.4%

[a] Transient and reversible changes

first course of therapy and attaining PR in the second or third course, indicating a very rapid response to this therapy.

Table 3 shows the side effects during the first course of therapy. Alopecia occurred in all cases, vomiting in 16.2%, stomatitis in 32.4%, and neuropathy in 24.3%. Out of 37 cases, 14 (37.8%) showed nonspecific ST-T, VPC, and low voltage on the electrocardiogram, and all the changes were transient and reversible except for the 2 cases of myocardial damage. Both of these, one of whom had a previous episode of atrial fibrillation (AF) and sustained myocardial damage with AF after the first injection of adriamycin (27.4 mg/m^2) while the other had a low performance status (30%) and sustained myocardial damage after the second injection of adriamycin (total 102.7 mg/m^2), had been exposed to large doses of ^{60}Co irradiation in the vicinity of the heart among other areas. It seems that myocardial damage occurred because of the sensitization to cardiotoxicity of adriamycin by the prior radiation to the heart area, and not the accumulation of adriamycin.

Leukopenia of under 2000/mm^3 was found in 29.7% of cases, but this did not exceed 8.1% for those with leukopenia under 1000/mm^3. Also, compared with the leukopenia, the thrombopenia was mild, with thrombopenia of less than 100000/mm^3 seen in 8.1% and indicating rapid recovery (Table 4). For those cases with leukopenia less than 2000/mm^3 the dose of adriamycin was reduced.

Discussion

The three principles for the use of drugs in combination chemotherapy, as documented by Comis et al. [7], are: (1) Each drug should be active against tumors when used alone; (2) the drugs should have different mechanisms of action; and (3) the toxic effects of the drugs should not be the same, so that each drug can be administered at or near its maximum tolerated dose.

Table 4. Hematological toxicity of VEMFAH therapy

Leukopenia		
< 2000/mm^3	11/37	29.7%
< 1000/mm^3	3/37	8.1%
Thrombopenia		
< 100000/mm^3	3/37	8.1%
< 50000/mm^3	3/37	8.1%
Anemia (Hb)		
< 8.0 g/dl	6/37	16.2%

The drugs used in our study are widely recognized as having a high antitumor activity. According to Carter [5, 6] and Carbone et al. [4], the average response rates of the drugs used singly are: cyclophosphamide 34% (25%–50%); 5-fluorouracil 26% (5%–65%); methotrexate 34% (11%–54%); vincristine 21% (10%–40%); and adriamycin 40% (13%–100%).

Also, it is considered that the action of each drug is different: the action point of the cell cycle is thought to be the S phase for methotrexate and 5-fluorouracil, cycle-nonspecific for cyclophosphamide and adriamycin, and the G_2 phase for vincristine.

In L1210 mouse leukemia, the combination of adriamycin plus 5-fluorouracil showed a synergistic effect, and the combinations of adriamycin plus methotrexate, adriamycin plus vinblastine, and adriamycin plus cyclophosphamide had additive effects [16].

We believe that each of the drugs used in our VEMFAH therapy had a different mechanism of action and that each was administered in its optimum dose. Also, with regard to side effects the doses used in the combination regimen were administered with due consideration for the possibility of bone marrow suppression by adriamycin, cyclophosphamide, and methotrexate, less severe bone marrow suppression by vincristine and 5-fluorouracil, cardiotoxicity due to accumulation in the case of adriamycin, and gastrointestinal toxicity in that of methotrexate, adriamycin, and 5-fluorouracil.

Since its introduction by Greenspan's group [12, 13], combination chemotherapy has produced remarkable responses in recent years. The 88% response rate reported with the five-drug combination CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone) by Cooper [8] in 1969 was particularly striking. In addition, further clinical trials have been carried out recently with wide-range combination chemotherapy including adriamycin. Creech et al. [9] reported that although adriamycin was certainly effective, its side effects were severe and it should be used as a second-line therapy because, compared with CAMF, CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) was not inferior in either response or survival time. However, Bull et al. [3] compared CMF with CAF and found that CMF had fewer side effects and there was no difference in response duration between CMF and CAF, but that CAF was significantly more effective than CMF. When Muss et al. [19] compared CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone) and CAFVP (cyclophosphamide, adriamycin, 5-fluorouracil, vincristine, and prednisone) they found that CAFVP was significantly superior in producing a response and increasing survival time, and they reported that adriamycin should be used as a first-line therapy. Also, Hirshaut et al. [15] reported long-term remission of breast cancer achieved with a six-drug combination therapy including adriamycin.

We took into consideration the fatal nature of the disease and the response to the various anticancer drugs currently in use when given singly, and if there were no notable serious side effects we based our treatment design on observations recorded in the treatment of acute leukemia: 'at the beginning of induction therapy leading into remis-

sion, reduction of the tumor size is a positive indication of extended survival time.' Accordingly, we devised our six-drug intensive and intermittent chemotherapy VEMFAH with adriamycin as the main drug, and found a high 77.1% response rate (median response duration; 52 weeks or 12 months). To avoid the bias that could be introduced because patients with better performance status both have a higher probability of responding and would have lived longer anyway because of their less aggressive disease, we applied the criterion that each patient had received at least two courses of therapy when we compared the 50% survival time of responders with that of nonresponders. In 32 patients who received more than two courses of VEMFAH therapy, the 50% survival time of the responders (27.0 months) was strikingly longer than that of nonresponders (10.3 months; $P < 0.05$). This result is superior or at least as good as that with other combination chemotherapies with adriamycin, such as CAMF (response rate, 62%; median survival time of CR + PR, 20 months) [9], CAFVP (58%; 50% survival time of CR + PR, 33 months) [19], CAF (82%; 50% survival time of CR + PR, 27.2 months) [3], VAC (72% median survival time of CR + PR, 24 months) [20] and Hirshaut's regimen (71%; median survival time of CR + PR, 36 months) [15]. Furthermore, the period from the initiation of VEMFAH therapy to the induction of PR was shortened, and we therefore recommend that adriamycin should be administered as a first-line therapy against recurrent advanced breast cancer.

From this study we conclude that VEMFAH therapy, a six-drug combination including adriamycin, is effective, can be administered for long periods, and may be an active chemotherapy for recurrent advanced breast cancer.

References

1. Arcamone F, Cassinelli G, DiMarco A, Gaetani M (1970) Adriamycin, a new antibiotic substance. Chem Abstr 72: 20610 (abstract 20607t)
2. Broder LE, Tormey DC (1974) Combination chemotherapy of carcinoma of the breast. Cancer Treat Rev 1: 183
3. Bull JM, Tormey DC, Li SH, Carbone PP, Falkson G, Blom J, Perlin E, Simon R (1978) A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 41: 1649
4. Carbone PP, Bauer M, Band P, Tormey DC (1977) Chemotherapy of disseminated breast cancer, current status and prospects. Cancer 39: 2916
5. Carter SK (1972) Single and combination nonhormonal chemotherapy in breast cancer. Cancer 30: 1543
6. Carter SK (1976) Integration of chemotherapy into combined modality treatment of solid tumors. VII: Adenocarcinoma of the breast. Cancer Treat Rev 3: 141
7. Comis RL, Carter SK (1974) A review of chemotherapy in gastric cancer. Cancer 34: 1576
8. Cooper RG (1969) Combination chemotherapy in hormone-resistant breast cancer. Proc Am Assoc Cancer Res 10: 15 (abstract 57)
9. Creech RH, Catalano RB, Harris DT, Engstrom PF, Grotzinger PJ (1979) Low dose chemotherapy of metastatic breast cancer with cyclophosphamide, adriamycin, methotrexate, 5-fluorouracil (CAMF) versus sequential cyclophosphamide, methotrexate, 5-fluorouracil (CMF) and adriamycin. Cancer 43: 51
10. DiMarco A, Gaetani M, Scarpinato B (1969) Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. Cancer Chemother Rep 53: 33
11. Gehan E (1965) A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 52: 203
12. Greenspan EM (1966) Combination cytotoxic chemotherapy in advanced disseminated breast carcinoma. J Mt Sinai Hosp 33: 1
13. Greenspan EM, Fieber M, Lesnick G, Edelman S (1963) Response of advanced breast carcinoma to the combination of the antimetabolite, methotrexate, and the alkylating agent, thio-TEPA. J Mt Sinai Hosp 30: 246
14. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD (1971) Assessment of response to therapy in advanced breast cancer. International Union against Cancer, Geneva
15. Hirshaut Y, Kesselheim H (1979) Long-term remission of breast cancer achieved with 6-drug combination chemotherapy. Am Soc Clin Oncol 20: 386 (abstract C-394)
16. Hoshino A, Kato T, Amo H, Ota K (1972) Antitumor effects of adriamycin on Yoshida rat sarcoma and L1210 mouse leukemia – Cross-resistance and combination chemotherapy. In: International symposium on adriamycin. Springer, Belin Heidelberg New York, p 75
17. Hoshino A, Nagura E. Ohsugi J, Ohguchi S, Hashizume M, Yamasaki K, Hirota T, Niinomi F (1978) Effects of multiple combination chemotherapy with vincristine, Endoxan, methotrexate, 5-fluorouracil, adriamycin and prednisolone ("VEMFAH") for advanced breast cancer. Jpn J Cancer Chemother 5: 215
18. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457
19. Muss HB, White DR, Richards F, II, Cooper MR, Stuart JJ, Jackson DV, Rhyne L, Spurr CL (1978) Adriamycin versus methotrexate in five-drug combination chemotherapy for advanced breast cancer. A randomized trial. Cancer 42: 2141
20. Rainey JM, Jones SE, Salmon SE (1979) Combination chemotherapy for advanced breast cancer utilizing vincristine, adriamycin, and cyclophosphamide (VAC). Cancer 43: 66

Received December 10, 1984/Accepted March 28, 1985