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Sequence for Developing Optimal Combination Chemotherapy of Metastatic Breast Cancer

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Abstract—*A prospective clinical trial was carried out in order to develop an optimal sequential combination chemotherapy for metastatic breast cancer.* (1) *One hundred and ninety-three patients were treated with* 2, 3 *or* 5 *agents as primary chemotherapy. The* 2 *or* 3 *drug regimens, (cyclophosphamide,* 5*-fluorouracil ± prednisone) were effective as the* 5 *drug therapy (cyclophosphamide,* 5*-fluorouracil, methotrexate, vincristine, prednisone):* 28 *of* 85 (33%), 22 *of* 52 (42%) *and* 23 *of* 56 (41%) *responded* ($P > 0.1$). (2) *One hundred and forty-two patients who failed or relapsed on* 2 *or* 3 *drugs received as secondary therapy either* 5 *drugs, or methotrexate, vincristine ± prednisone, demonstrating that the* 5 *drug regimen retains its effectiveness as secondary therapy* (47%) *and cyclophosphamide and* 5*-fluorouracil may act as potentiating agents in the secondary* 5 *drug combination.* (3) *Adriamycin–cyclophosphamide given as tertiary therapy in* 12 *patients secured more responses* (42%) *The use of sequential chemotherapy of primary* (2 *or* 3 *drugs), followed by secondary* (5 *drugs) and adriamycin–cyclophosphamide as tertiary regimen provides further responses and prolongs survival.*

INTRODUCTION

THE CURRENT combination chemotherapy programs, in spite of using 5 and 6 agents at one time have not significantly improved the response rate and duration of remission and survival in patients with metastatic breast cancer [1–3]. Furthermore, after failure or relapse of the disease when all active drugs have been exhausted, further management is comprised and is limited to less effective or investigational drugs. Our efforts have been directed toward avoiding premature exhaustion of therapeutic modalities and developing optimal sequential combination therapy.

MATERIALS AND METHODS

A prospective clinical trial was carried out in postmenopausal patients with progressive, measurable metastatic disease in order to provide an alternate strategy for combination chemotherapy capable of increasing the number of responses and prolong survival.

(1) In the initial study 193 patients were treated in three consecutive clinical trials with 5, 3 or 2 agents as primary chemotherapy: (a) Fifty-six patients received 5 drug combination with 5-fluorouracil (F) 500 mg, methotrexate (M) 25 mg and vincristine (V) 1 mg intravenously (i.v.) weekly; 100 mg cyclophosphamide (Cytoxan-C) orally and prednisone (P) orally tapered weekly from 40 to 10 mg as maintenance dose. (b) Fifty-two patients were given 3 drug therapy as intermittent regimen: C, 4 mg/kg and F, 8 mg/kg i.v. daily for 5 day courses every 5 weeks. Prednisone was given orally daily, tapered weekly from 40 to 10 mg as maintenance dose. (c) Eighty-five patients received 2 drug therapy (CF) as described in the 3 drug regimen, minus prednisone.

(2) In a following study, a total of 142 patients who failed or relapsed on primary chemotherapy with 2 (CF) or 3 drugs (CFP) were treated subsequently in three consecutive carefully designed clinical trials with either 5 drugs (CFMVP) or MV or MVP, in order to determine the effectiveness of the 5 drug combination as secondary therapy. Another

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goal of this study was to find out if prior used drugs (CF) were required as potentiating agents on the newly added drugs (MV ± P) in the 5 drug combination.

(3) Twelve patients who failed or relapsed on secondary therapy are receiving at the present time C, 400 mg/m^2 and adriamycin (A), 40 mg/m^2 i.v. courses every 4 weeks as tertiary program of combination chemotherapy.

Progression of disease was assessed by the criteria of the response to therapy in advanced breast cancer outlines by the International Union Against Cancer [4].

RESULTS

(1) *Combination of five, three or two agents as primary chemotherapy*

Our results demonstrate that all regimens used in this study are effective therapy for metastatic breast cancer and no significant differences were observed among the three combinations ($P>0.1$): 23 of 56 (41%) demonstrated objective response in the 5 drug group; 22 of 52 (42%) and 28 of 85 (33%) responded in the 3 and 2 drug groups respectively (Table 1) with a similar mean duration of remission of 8–8.5 months [5].

(2) *Five drug secondary therapy following 2 or 3 drugs*

In a following study, 22 patients who received prior CF or CFP and failed or relapsed were treated subsequently with 5 drugs (CFMVP) and 10 of 22 (45%) demonstrated objective response with a mean duration of remission of 8.5 months. This study demonstrated also, that the 5-agent combination could be used after the 2 or 3 drug therapy and still retain its effectiveness.

Potentiating role of previously administered agents in the combination chemotherapy

Following these observations a further study was designed to determine whether the effectiveness of the 5 drug combination after CF or CFP was due only to MV ± P, or whether CF were still required as potentiating agents. In other words, we wanted to test if CF had an enhancing effect on the newly added drugs (MV ± P).

In this study, a total of 120 postmenopausal women with progressive measurable metastatic breast cancer and comparable extent of disease, who received prior CF or CFP were treated in 3 consecutive clinical trials with either MV, MVP or CFMVP [6]. In a first study 25 patients received MV and 3 patients responded (12%). Thirty patients received MVP and objective responses were seen in 4 of 30 patients (13%). In an ongoing study 65 patients received 5 drug combination and 31 demonstrated objective response (48%) (Table 2). Prior chemotherapy with either 2 or 3 drugs in the present series did not influence the response to any of the following chemotherapy regimens (Table 3). The 5 drug combination is more effective in the patients who responded to prior CF or CFP than those who have failed (Table 4). When the prior responders to CF received the 5 drug therapy 7 of 11 (64%) had an additional response. Of the 21 CF failures, 7 responded to the subsequent 5 drug combination. The same trend was observed in the CFP primary chemotherapy group. Of the 15 prior responders to CFP, 10 showed an additional response (67%) to subsequent 5 drug combination. Of the 18 prior failures, 7 responded to the 5 drug therapy. Duration of remission measured from the start of therapy to the end of response was similar in each group with a mean of 8.2 months.

(3) *Cyclophosphamide–adriamycin as tertiary combination chemotherapy*

At the present time we are using CA combination after 5 drug regimen as a tertiary program securing more responses. Of 12 patients entered, 5 of 7 evaluable are responding.

DISCUSSION

Our present results shows that 2 or 3 drug chemotherapy (CF or CFP) is as effective a primary treatment for metastatic breast cancer as is the 5 drug combination of CFMVP, while causing less toxicity [7]. In a prior randomized trial we have shown that CFP presented an advantage over adriamycin or adrenalectomy as the first modality of systemic therapy [8]. Furthermore we have found that the five-agent program retains its effectiveness even if used after CF or CFP. The 5 drug combination is more effective in the patients who responded to prior CF or CFP than those who have failed. The 5 drug combination of CFMVP was significantly more effective than MV or MVP regimens used after the patient has had CF or CFP ($P<0.001$). The combination of MV or MVP

when given alone after CF or CFP and at the same dosages and schedule as in the 5 drug regimen have a low level of activity. The dosage of methotrexate could be called sub-optimal, yet it is the same dosage that had proved effective in the 5 drug regimen. A recent experimental study done by R. Bender *et al.* [9] demonstrated a lack of therapeutic synergism between vincristine and methotrexate in L 1210 murine leukemia *in vivo*, which might explain the poor results obtained in our clinical human trial with combination of MV. The addition of prednisone to methotrexate–vincristine did not increase the activity of the combination. F. Rosner *et al.* [10] showed that in rapidly growing cell

Table 1. *Dominant metastasis in responders; 5 drugs vs 3 drugs vs 2 drugs*

	No. of responders/total patients					
Specific site	CFMVP		CFP		CF	
Visceral	20/47	(42)	19/45	(42)	18/53	(34)
Central nervous system	5/9		6/10		0/2	
Liver	4/13		6/23		9/26	
Pulm-pl. peric. eff.	10/21		5/7		8/21	
Mediast. esoph. obst.	1/1		1/4		0/2	
Perit.-retrop.	0/3		1/1		1/2	
Osseous	2/6		2/6		5/20	
Soft tissue	1/3		1/1		5/12	
Totals	23/56	(41)	22/52	(42)	28/85	(33)

$P > 0.1$.
Numbers in parentheses = %.

Table 2. *Dominant metastasis in responders to CFMVP, MV, MVP following CF or CFP*

	No. of responders/total patients					
Specific site	CFMVP		MV		MVP	
Visceral	24/53		1/15		2/15	
Central nervous system	6/10		0/1		2/5	
Liver	8/20		0/5		0/1	
Pulm-pl. peric. eff.	9/19		1/8		0/9	
Mediast. esoph. obst.	1/3		0/1		—	
Perit.-retrop.	0/1	—	—			
Osseous	6/11		1/8		0/10	
Soft tissue	1/1		1/2		2/5	
Totals	31/65	(48)	3/25	(12)	4/30	(13)

$P < 0.001$.
Numbers in parentheses = %.

Table 3. *Previous chemotherapy in responders*

	No. of responders/total patients					
Previous chemotherapy	CFMVP		MV		MVP	
CF	14/32	(44)	2/13	(15)	2/14	(14)
CFP	17/33	(51)	1/12	(8)	2/16	(12)
Totals	31/65	(48)	3/25	(12)	4/30	(13)

Numbers in parentheses = %.

Table 4. Response to secondary 5 drug regimen in previous chemotherapy responders

Previous chemotherapy	No. of responders/ total patients CFMVP	
CF		
Responders	7/11	(64)
Non-responders	7/21	(33)
CFP		
Responders	10/15	(67)
Non-respondrrs	7/18	(39)

Numbers in parentheses = %.

culture, resistant to vincristine, the addition of prednisolone restores their sensitivity to vincristine, by retaining more cells in G_1. However, the combination of these two drugs was no more effective than vincristine alone in stable cell population, where no further kill was achieved by adding prednisolone.

From our data it is possible to ascertain that the responses to 5 drug secondary therapy following CF or CFP were not due only to MVP alone. The data suggests that cyclophosphamide and 5-fluorouracil may play a part in enhancing the drug effect of methotrexate, vincristine and prednisone given as secondary chemotherapy in the 5 drug regimen. Of course, these data do not tell us if this enhancing effect is peculiar to breast cancer and to these particular chemotherapy regimens or if it can be applied more generally. The exploitation of the possible potentiating effect of previously used agents in subsequent chemotherapy regimens in combination with newly added active drugs might represent an improvement in the treatment options now available. These observations are important considerations in employing multiple agent programs sequentially in advanced breast cancer. Perhaps more important than the immediate response rate to therapy is the total survival and quality of life. Our present data demonstrates that the survival in the group treated sequentially with CF of CFP as the primary chemotherapy and CFMVP as the secondary therapy was significantly longer (9.2 months more) than in the prior personal series of 56 patients treated with the same 5 drug regimen as the first combination chemotherapy.

Based on these experiences we conclude that the first choice for chemotherapy in estrogen receptor-negative tumors or in patients with positive estrogen and prior hormonal manipulations should be the 2 or 3 drug regimen, CF or CFP, because of their effectiveness and relatively low toxicity. After failure or relapse, CFMVP should then be employed, as a valuable effective secondary program. Cyclophosphamide–adriamycin combination used as a tertiary regimen offers more responses.

The use of subsequent regimens offers an alternate strategy for developing an optimal sequential combination chemotherapy providing the opportunity for further responses and prolong survival.

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