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The modulating effects of flurbiprofen on adriamycin plus vincristine or vindesine in the treatment of advanced breast cancer

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Summary. To assess the modulating effects of a non-steroidal anti-inflammatory drug on chemotherapeutic agents, 183 patients with advanced breast cancer have been treated in a randomised study with flurbiprofen or placebo and adriamycin plus a vinca alkaloid. To assess the efficacy of the new vinca alkaloid, vindesine, in breast cancer, patients were further randomised to receive vindesine or vincristine. The overall response rate in evaluable patients was 57%, and the median duration of response in the different treatment groups varied from 6 to 10 months. Response rates and toxicity in vindesine- and vincristine-treated patients were similar, although with vindesine neurotoxicity was slightly lower. Flurbiprofen did not improve the response rate or reduce the toxicity of adriamycin plus vinca alkaloid.

Introduction

Since the introduction of adriamycin there have been few worthwhile advances in the chemotherapeutic management of breast cancer, and new approaches are sorely needed. Possible approaches include the minimisation of toxicity from existing drugs and the introduction of new drugs. In experimental animals, inhibitors of prostaglandin synthesis such as indomethacin and flurbiprofen have accelerated haematopoietic and gastrointestinal cell recovery following treatment with alkylating agents [12] and irradiation [13] without inhibiting the anti-tumour effect. Prostaglandin E2 is known to inhibit the maturation of murine haematopoietic stem cells [9], and it is therefore possible that inhibition of prostaglandin synthesis may accelerate marrow recovery following cytotoxic suppression. In addition, prostaglandins have been implicated in the osteolytic process associated with bone metastases [1, 7], and therefore the inhibition of tumour-induced osteolysis may promote the resolution of bone metastases. Although anti-inflammatory agents alone have no prophylactic or therapeutic effect on bone metastases in humans [14] little information is available concerning their interaction with cytotoxic agents. In this study the interaction between flurbiprofen and adriamycin plus vinca alkaloid has been assessed in relation to toxicity and anti-tumour effect.

Vinca alkaloids have long been included in cytotoxic combinations for metastatic breast cancer. As a single agent vincristine is reported to produce responses in 21% of patients [5]. Vindesine is a new semi-synthetic vinca alkaloid with similar neurotoxicity to vincristine but greater marrow toxicity [3]. The data concerning vindesine and breast cancer are limited, but the reported response rates have varied from 26%–29% [6, 15, 17]. To clarify the role of vindesine in breast cancer patients have been randomised to receive vindesine or vincristine together with adriamycin.

Patients and methods

In all, 183 patients with histologically confirmed metastatic breast cancer were entered into the study between April 1979 and October 1983. Patients were randomly allocated to receive vincristine, adriamycin, and flurbiprofen (46 patients); *or* vincristine, adriamycin, and placebo (46 patients); *or* vindesine, adriamycin, and flurbiprofen (44 patients); *or* vindesine, adriamycin, and placebo (47 patients). Analysis of results was based on comparison of the 92 patients recieving vincristine and the 91 patients receiving vindesine. Similarly, the 90 patients receiving flurbiprofen with their chemotherapy were compared with the 93 patients receiving placebo with their chemotherapy. Patients in the four treatment groups were not significantly different in terms of age, disease-free interval, menopausal status, previous chemotherapy, total number of disease sites, and number of visceral disease sites (Table 1). Previous exposure to adriamycin, vinca alkaloids, or flurbiprofen rendered patients ineligible for study.

All patients had assessable disease, but only 140 of the 183 patients randomised had an adequate trial of therapy (i.e., three cycles of therapy of disease progression after commencing treatment) and were evaluable for response. Of the 43 patients who were not evaluable, 31 died within 12 weeks of commencing therapy, 8 withdrew from treatment after receiving less than three treatment cycles, 3 patients had inadequate documentation of disease response, and 1 patient was lost to follow up. All patients were assessed for toxicity every 4 weeks, but 5 patients were not included in the analysis of toxicity because of inadequate documentation.

Response to treatment was assessed according to UICC criteria [8]. A response was recorded when unidimensional lesions decreased by at least 50% and, for bidimensional lesions, when the product of perpendicular diameters decreased by at least 50%. Recalcification of

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Table 1. Clinical characteristic of 183 patients who received vincristine or vindesine in combination with adriamycin together with placebo or flurbiprofen

	Vincristine	Vindesine	Flurbiprofen	Placebo	Total
Number randomised	92	91	90	93	183
Number evaluable for response	72	68	63	77	140
Age range (mean)	28–73 (53)	29–73 (53)	29–70 (54)	28–73 (53)	
Mean number of disease sites	2.4	2.6	2.5	2.6	2.5
Mean number of visceral sites	1.4	1.7	1.6	1.5	1.5
Menopausal status: Pre- and Peri-	10	16	12	14	
Post-	82	75	78	79	
Median disease-free interval (months)	16	20	17	19	
Previous chemotherapy	18	18	17	19	
Previous endocrine therapy	71	67	67	71	
Median time from relapse to randomisation (months)	18	19	16	21	

osteolytic lesions was interpreted as a response in bone. Responses had to be maintained for at least 2 months.

Prior to treatment, for each patient clinical examination, haematology and biochemistry profiles, ECG, chest x-ray, and radiographic skeletal survey were performed. During the first cycle of treatment haematology profiles were performed at days 7 and 14 and thereafter 4-weekly. Clinical examination was repeated every 4 weeks and x-rays and biochemistry profiles were repeated 3-monthly, or more frequently if required. Other investigations performed for specific indications included bone and liver scintigraphy, liver ultrasonography, and bone marrow examination.

Patients were randomised to receive either vincristine or vindesine, and flurbiprofen or placebo. All patients received adriamycin. Drug doses and scheduling were as follows: adriamycin 40 mg/m^2 as an IV bolus on days 1 and 8; vincristine 1.4 mg/m^2 (maximum 2 mg) or vindesine 3 mg/m^2 as an IV bolus on days 1 and 8; flurbiprofen or placebo 100 mg PO three times daily on days 1–28. The treatment cycle was repeated every 28 days. Adriamycin and vinca alkaloid were discontinued once the cumulative dose of adriamycin reached 550 mg/m^2, and therapy was continued with a 28-day cycle of chlorambucil 10 mg PO on days 1–14, methotrexate 35 mg/m^2 IV on days 1 and 8, and 5-fluorouracil 600 mg/m^2 IV on days 1 and 8. Flurbiprofen/placebo continued despite the change in chemotherapy.

Results

In evaluable patients complete and partial response rates were 15% and 39%, respectively, giving on overall response rate of 54% (Table 2). Stable disease was recorded in 16% of patients, and 29% experienced tumour progression despite treatment. The complete, partial, and overall response rates in the four treatment groups were not significantly different. Again no differences were observed when overall response rates were assessed in terms of vincristine versus vindesine (50% and 59%, respectively) and flurbiprofen versus placebo (52% and 56%, respectively). The response rates in the treatment groups in all randomised patients (irrespective of evaluability) paralleled the results seen in evaluable patients.

Duration of response for the different treatment groups is depicted in Figs. 1 and 2. The median response duration for vincristine versus vindesine and flurbiprofen versus placebo are the same.

Table 2. Objective response rates of patients receiving vincristine versus vindesine in combination with adriamycin together with placebo or flurbiprofen

	Vincristine	Vindesine	Flurbiprofen	Placebo	Total
Patient numbers					
All patients randomised	92	91	90	93	183
Evaluable patients	72	68	63	77	140
Complete response					
All patients randomised	12 (13%)	9 (10%)	7 (8%)	14 (15%)	21 (11%)
Evaluable patients	(17%)	(13%)	(11%)	(18%)	(15%)
Partial response					
All patients randomised	24 (26%)	31 (34%)	26 (29%)	29 (31%)	55 (30%)
Evaluable patients	(34%)	(46%)	(41%)	(38%)	(39%)
Complete + partial response					
All patients randomised	36 (39%)	40 (44%)	33 (37%)	43 (46%)	77 (42%)
Evaluable patients	(50%)	(59%)	(52%)	(56%)	(54%)

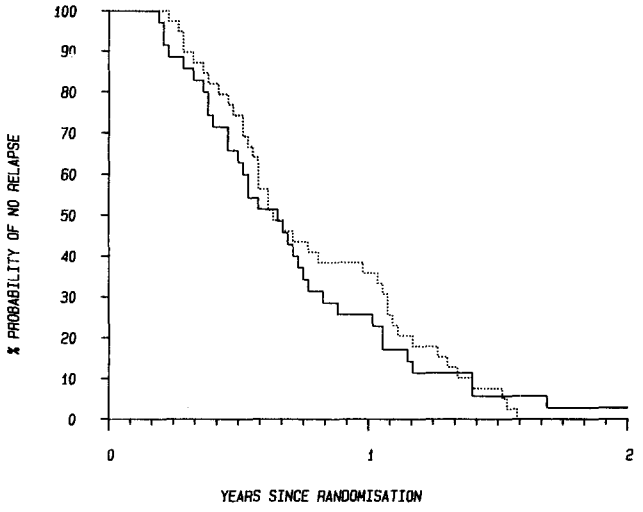

Fig. 1. Duration of response from date of randomisation to evidence of progression for 36 patients responding to vincristine combination (———) versus 40 patients responding to vindesine combination (·····)

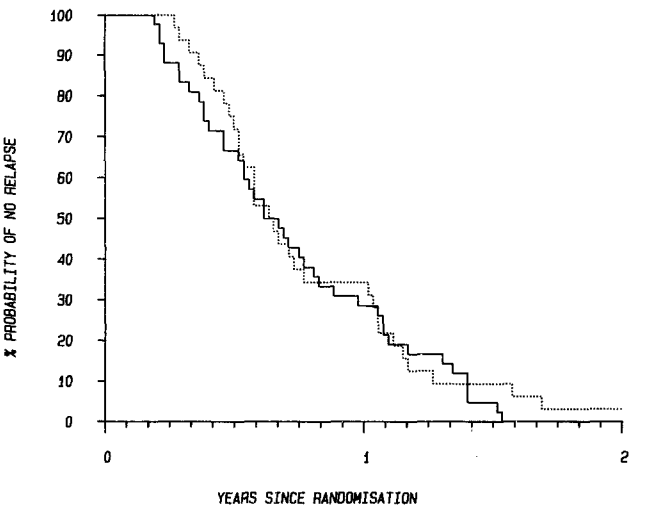

Fig. 2. Duration of response from date of randomisation to evidence of progression for 43 patients responding to combination chemotherapy plus placebo (———) versus 33 patients respondign to combination chemotherapy plus flurbiprofen (·····)

Table 3. Objective response by site of disease in patients receiving vincristine versus vindesine in combination with adriamycin together with placebo or flurbiprofen

	Vincristine	Vindesine	Flurbiprofen	Placebo	Total
Local recurrence	18/31	14/22	14/24	18/29	32/53 (60%)
Skin (not local recurrence)	10/21	14/22	10/18	14/25	24/43 (56%)
Lymph nodes	11/22	17/23	10/18	18/27	28/45 (62%)
Lung, parenchyma	8/14	7/18	5/13	10/19	15/32 (47%)
Lung, lymphangitis	2/6	2/7	0/1	4/12	4/13 (31%)
Liver	12/18	13/22	11/24	14/16	25/40 (62%)
Bone	1/14	7/20	4/14	4/20	8/34 (24%)

Table 4. Haematological toxicity in 178 patients who received vincristine versus vindesine in combination with adriamycin together with placebo (90) or flurbiprofen (88)

	Vincristine (88)	Vindesine (90)	Flurbiprofen (88)	Placebo (90)	Total (178)
Thrombocytopenia					
$20-99 \times 10^9/l$	15 (17%)	11 (12%)	12 (14%)	14 (16%)	26 (15%)
$<20 \times 10^9/l$	4 (5%)	0	1 (1%)	3 (3%)	4 (2%)
Leucopenia					
$1-3 \times 10^9/l$	28 (32%)	35 (39%)	28 (32%)	35 (39%)	63 (35%)
$<1 \times 10^9/l$	5 (6%)	10 (11%)	8 (9%)	7 (8%)	15 (8%)

An analysis of response by site is presented in Table 3. Response was greatest in soft tissue sites and poorest in bone. The small numbers of patients in the various treatment groups precludes any comments about differential response rates by site, but it is worth noting that flurbiprofen-treated patients did not show a significantly better response in bone than placebo-treated patients.

The actuarial survival curves for patients in the four treatment groups are shown in Figs. 3 and 4. There was no significant survival difference between vincristine- and vindesine-treated patients or between flurbiprofen and placebo-treated patients. However, the median actuarial survival was significantly longer for responding patients (14 months) than for non-responding patients (6 months).

The major toxicities associated with treatment are summarised in Tables 4 and 5. Haematological toxicity (Table 4) was most frequently manifest as leucopenia (35%). Severe leucopenia (WBC $< 1 \times 10^9/l$) occurred in 15 patients (8%), 6 of whom developed signs and symptoms of septicaemia requiring IV antibiotic therapy. Thrombocytopenia was less of a problem (15%), with only 2% of patients having a platelet count of less than $20 \times 10^9/l$. Haematological toxicity was similar in patients receiving flurbiprofen versus placebo and vindesine versus vincristine.

The incidence of non haematological toxicity is summarized in Table 5. Apart from a marginal reduction in neuropathy the toxicity for patients receiving vindesine versus vincristine was similar. With regard to patients re-

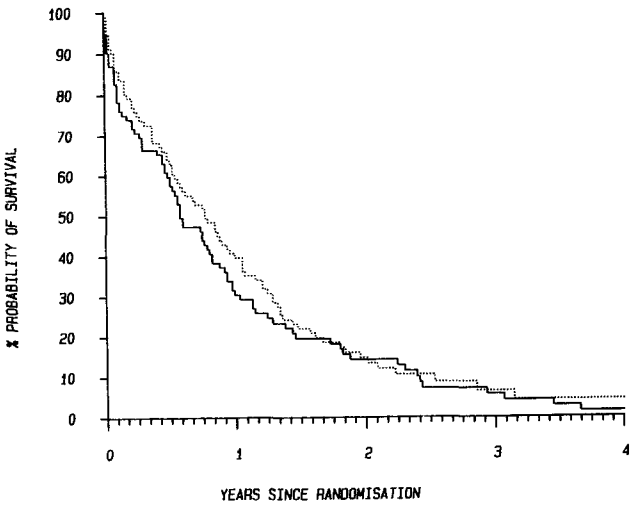

Fig. 3. Survival from date of randomisation to death for 92 patients receiving vincristine combination (———) versus 91 receiving vindesine combination (·····)

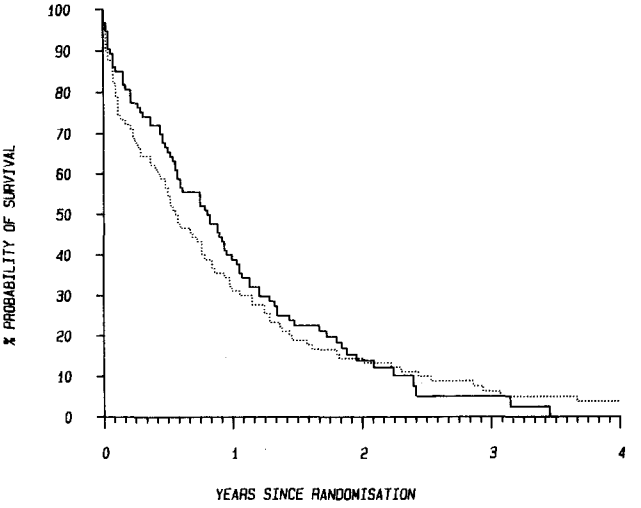

Fig. 4. Survival from date of randomisation to death for 90 patients receiving combination chemotherapy plus flurbiprofen (·····) versus 93 patients receiving combination chemotherapy plus placebo (———)

Table 5. Percentage incidence of toxic responses to treatment in 178 patients who received vincristine (88) versus vindesine (90) in combination with adriamycin together with placebo (90) or flurbiprofen (88)

	Vincristine (88)				Vindesine (90)				Flurbiprofen (88)				Placebo (90)			
	Mild	Mod.	Mark.	Total	Mild	Mod.	Mark.	Total	Mild	Mod.	Mark.	Total	Mild	Mod.	Mark.	Total
Nausea	28%	10%	11%	50%	26%	15%	20%	61%	26%	14%	9%	49%	28%	11%	23%	62%
Vomiting	25%	5%	12%	42%	14%	17%	11%	43%	14%	10%	7%	31%	25%	11%	17%	55%
Alopecia	7%	5%	40%	52%	10%	6%	41%	58%	7%	6%	37%	51%	10%	5%	43%	59%
Neuropathy	23%	15%	9%	47%	17%	10%	9%	36%	11%	15%	9%	35%	28%	10%	9%	48%
Stomatitis	11%	11%	10%	33%	12%	15%	8%	35%	10%	17%	8%	35%	14%	9%	10%	33%
Constipation	6%	6%	5%	16%	10%	8%	5%	23%	10%	5%	5%	19%	6%	9%	5%	19%
Dose reduction		29 (33%)				32 (36%)				28 (32%)				33 (37%)		
Cessation of treatment		4 (5%)				0 (0%)				3 (3%)				1 (1%)		

ceiving flurbiprofen versus placebo the incidence of alopecia, stomatitis, and constipation was similar. Although the incidence of nausea, vomiting, and neuropathy appeared lower for patients receiving flurbiprofen versus placebo, these differences were not significant. There is no evidence from these data that flurbiprofen reduces normal tissue toxicity. The numbers of patients requiring dose reduction because of toxicity were similar in all groups, and few patients withdrew from treatment because of toxicity.

Discussion

There is no evidence from this study that the toxicity and antitumour effect of adriamycin and vinca alkaloids can be advantageously modified by the concurrent administration of flurbiprofen. In particular, haematopoietic and gastrointestinal toxicities were similar in flurbiprofen- and placebo-treated patients. Those animal studies suggesting amelioration of chemotherapy toxicity by anti-inflammatory drugs [12] were all based on alkylating agents. Unfortunately, our previous experience had shown that a combination of vincristine and adriamycin had given the best response with acceptable toxicity for patients requiring treatment with cytotoxic chemotherapy. On clinical grounds, this combination was therefore considered necessary for this study. It is possible that the toxicity reduction by anti-inflammatory drugs is specific for certain cytotoxic drugs and the negative result with adriamycin/vinca alkaloid does not exclude a possible beneficial effect with other classes of drugs. An analogy can be drawn with the use of alkylating agent priming where the toxicity reduction is clearly drug specific [10, 11]. It is also possible that inhibitors of prostaglandin synthesis other than flurbiprofen may improve the therapeutic index of cytotoxic agents in breast cancer, and further studies will be required to evaluate this. The failure of flurbiprofen to enhance the anti-tumour effect of adriamycin/vinca alkaloid reflects the inconsistency of this effect in experimental animals [12, 13]. Even though there are theoretical grounds for believing that prostaglandin inhibitors may promote the resolution of bone metastases, this study fails to lend support to this hypothesis, because bone response was very similar in the flurbiprofen and placebo groups.

The overall response rate and duration of response in this study are similar to those reported by other investigators working with adriamycin plus vincristine [4, 16]. The pattern of response by site is also consistent with previous experience, in that bone metastases and lymphangitis carcinomatosa are less responsive. The anti-tumour activity of vincristine and vindesine appears to be broadly similar, and toxicity was not appreciably different except possibly for neurotoxicity. Vindesine has a shorter plasma half-life than vincristine, and when it was first introduced for clinical use it was hoped that this might be reflected in diminished neurotoxicity; however, studies so far have not shown any major difference from vincristine. Vindesine is reputed to have greater haematological toxicity than vincristine [3], but in this study haematological toxicity was vera similar in both groups. Since the average dose of adriamycin per patient and per treatment course was not decreased in patients treated with vindesine, it appears that vindesine does not augment the marrow suppression due to adriamycin.

It seems that vindesine and vincristine have similar efficacy and toxicity in patients with advanced breast cancer. Some studies suggest incomplete cross resistance between these agents [2, 17], so their use in sequential chemotherapy combinations should be considered.

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