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Adriamycin Alone or Combined with Vincristine in the Treatment of Advanced Breast Cancer

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Abstract—*One hundred and nineteen women with advanced breast cancer treated previously by endocrine therapy but no prior chemotherapy were given adriamycin* 70 mg/m² *i.v. on day* 1 *of a* 3*-weekly cycle for* 8 *courses, followed by a regimen of cyclophosphamide, methotrexate and* 5*-fluorouracil (CMF) until relapse. They were allocated randomly to receive either no treatment (group A) or vincristine* 1.4 mg/m² *i.v. on days* 1 *and* 8 *during treatment with adriamycin (group AV). In* 107 *evaluable patients objective responses were seen in* 30/53 *patients* (57%) *in group A and in* 28/54 *patients* (52%) *in group AV. The projected dose of adriamycin received was* 78% *in group A and* 75% *in group AV; and* 60% *for vincristine in group AV. The subjective and haematological toxicity for adriamycin was similar in both groups, but* 65% *of patients treated with vincristine developed neurotoxicity. The median duration of objective regressions was the same for both groups* (7 months), *and the median time to failure was* 5 months *for group A and* 6 months *for group AV respectively. The median survival of the responders tended to be longer in group AV* (17.5 months) *than in group A* (13 months), *but this difference was not statistically significant* (P = 0.112). *It is concluded that there is no advantage therapeutically in combining vincristine and adriamycin in patients with advanced breast cancer.*

INTRODUCTION

ALTHOUGH adriamycin is probably the most active single cytotoxic drug for the treatment of advanced breast cancer, giving an objective response rate of about 40% [1, 2], it is still not clear whether or not other cytotoxic drugs contribute usefully to it in combinations [3, 4]. Several studies have suggested that by combining vincristine with adriamycin a higher regression frequency of 52–66% can be obtained [5–7], but these claims have never been confirmed in a prospective randomised clinical trial. Despite this, the combination of adriamycin plus vincristine (AV) has been used widely [7, 8] and tested in prospective controlled clinical trials with other agents [9, 10].

The object of this study was to assess more precisely the contribution of vincristine to adriamycin in the induction of regression of advanced breast cancer, the time to treatment failure, survival, drug toxicity and the ability to give the prescribed dose of adriamycin. A combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was chosen as subsequent chemotherapy after the safe cumulative dose of adriamycin had been prescribed, or as treatment for prior relapse, as the combination has been shown not to be cross-resistant with adriamycin and vincristine [6].

MATERIALS AND METHODS

Patients

Between May 1977 and January 1980, 119 women with metastatic breast cancer were entered in this prospective randomised clinical trial. Eligibility criteria include no prior chemotherapy for advanced breast cancer, no signs of abnormal cardiac function and the presence of progressive disease in evaluable lesions. Before entering this study 116 patients had had endocrine therapy (ovarian ablation in pre-menopausal women; androgens, oestrogens or antioestrogens in post-menopausal women; and, in some cases, subsequent hypophysectomy). Three pre-menopausal patients had chemotherapy as first-line treatment for advanced disease.

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Baseline investigations included a haematological and biochemical screen, radiological skeletal survey and/or isotopic bone scan, and an electrocardiograph. To be eligible patients had to have a minimum total white blood count of 2000/μl, a platelet count of ≥70,000/μl, blood urea ≤8 mmol/μl and bilirubin ≤50 μmol/l.

Randomisation

Patients were randomised to receive either adriamycin alone (group A) or adriamycin plus vincristine (group AV) for a maximum of 8 courses.

Chemotherapy

All patients received courses of chemotherapy as follows: adriamycin 70 mg/m² i.v. (maximum 120 mg) on day 1 of a 3-weekly cycle either alone or with vincristine 1.4 mg/m² i.v. (maximum 2 mg) on days 1 and 8, depending upon randomisation. In patients 60 yr old or more the dose of adriamycin was reduced to 60 mg/m² i.v. (maximum 100 mg).

After 8 cycles, or earlier in the event of disease progression, treatment was continued with cyclophosphamide 100 mg/m²/day p.o. (maximum 150 mg/day) on days 1–14 of a 4-weekly cycle with methotrexate 30 mg/m² i.v. (maximum 50 mg) and 5-fluorouracil 600 mg/m² i.v. (maximum 1000 mg) on days 1 and 8. In patients 60 yr old or more the dose of cyclophosphamide was reduced to a maximum 100 mg/day p.o., methotrexate to 20 mg/m² i.v. (maximum 40 mg) and 5-fluorouracil to 400 mg/m² i.v. (maximum 1000 mg). This regimen (CMF) was given at 4-weekly intervals until progression of disease.

The following dose modifications were adopted for cytotoxic drugs (except vincristine) in the presence of bone marrow suppression: for grade 1 toxicity [white blood count (WBC) 2000–3999/μl and/or platelet count 70,000–119,000/μl] 50% of the projected dose was given; for grade 2 toxicity (WBC ≤1999/μl and/or platelet count ≤69,999/μl) drugs were omitted until grade 1 toxicity was reached. If the platelet count was greater than 400,000/μl (vincristine-induced thrombocytosis), vincristine was omitted until it fell below this level. In the presence of hepatic metastases causing impairment of liver function, doses of adriamycin were reduced to 50% when the serum bilirubin level was between 23 and 50 μmol/l.

Assessment

Baseline lesions were selected for serial assessment. All visible lesions were photographed. Patients were followed-up at either 3- or 4-weekly intervals on day 1 of each cycle of treatment with a repeat assessment of palpable and visible baseline lesions, estimation of total WBC, platelet count and haemoglobin. Bone scintiscans and radiographs of chest and skeletal lesions were repeated 3-monthly and at treatment failure. Liver scans were done when indicated clinically.

Response criteria

The response to cytotoxic chemotherapy was assessed according to the criteria recommended by the UICC [11, 12], the records of patients being reviewed by two extramural independent assessors.

Response categories adopted were: complete response (CR): disappearance of all known disease. In the case of lytic bone metastases, these were shown radiographically to have recalcified; partial response (PR): a ≥50% decrease in the sum of the products of the perpendicular diameters of measurable lesions and objective improvement in other assessable lesions, these observations confirmed on two successive occasions at least 1 month apart, with no new lesions; no change (NC): lesions unchanged (i.e. <50% decrease or <25% increase in the size of measurable lesions) for at least 3 months; progressive disease (PD): progression of some or all lesions and/or appearance of new lesions.

Time to treatment failure (TTF)

Time to treatment failure was from start of chemotherapy to the date of documentation of progressive disease. In CR and PR, TTF is equivalent to the duration of response.

Survival

Survival was from date of start of chemotherapy to date of death, with follow-up to June 1982, when 16 patients were still alive with a median survival of 20 months from start of chemotherapy.

Statistical methods

Survival and time to treatment failure (TTF) were analysed by the log-rank method [13]. The significance between binary values was calculated by the chi-square test for one degree of freedom.

Performance criteria

A 0–4 grade scale was adopted [11]: grade 0: fully active; grade 1: ambulatory, light work; grade 2: ambulatory, capable of all self-care; grade 3: limited self-care, confined to bed or chair more than 50% of waking hours; grade 4: totally confined to bed or chair.

RESULTS

One hundred and nineteen patients were entered in this prospective controlled clinical trial. Ten patients were excluded from analysis because either they were found not to be eligible for this trial (9 patients) or the records were found

to be inadequate for assessment (1 patient). Two patients who died shortly after randomisation before chemotherapy was given were included for survival analysis, but not for the assessment of response. One hundred and seven evaluable patients form the subject of this report.

The characteristics of the two treatment groups (Table 1) were similar with regard to age at diagnosis and at start of chemotherapy. No significant disparity between post-operative disease-free interval and time interval between diagnosis and start of chemotherapy was observed. The performance status at the start of chemotherapy tended to be more favourable in group AV. Previous treatment for primary operable disease and subsequent endocrine management of advanced disease are summarised in Table 2, being similar in each group.

The objective response frequencies were 57% for group A and 52% for group AV respectively, with 1 complete response in group A and 2 in group AV (Table 3). Because of subsequent disease progression in some patients whilst on A or AV treatment, the response rates at the end of adriamycin therapy were markedly lower than the initial response (36% in group A vs 39% in group AV).

The objective response at sites of involvement are listed in Table 4, with similar results for lesions in breast, skin and lymph nodes. Pulmonary metastases tended to respond better in group AV (57%) than in group A (32%). A poor response of bone lesions was noted in both treatment arms (16% in A, 14% in AV).

The median duration of objective regressions was 7 months in both groups and median time to failure was 5 months in A and 6 months in AV ($\chi^2 = 0.0826$; $P < 0.77$). The median survival of all patients in group A was 10 months vs 14 months in group AV ($\chi^2 = 3.41$; $P = 0.064$) and the median survival time of responders 13 months for A and 17.5 months for AV. Despite this trend in favour of the AV group the survival curves were not significantly different ($\chi^2 = 2.51$; $P = 0.112$) (Fig. 1).

After CMF was started only 3 patients in group A and 1 patient in group AV achieved an improved response category.

Table 1. Characteristics of patients

	Group A	Group AV
No. of patients	53	54
Median age at diagnosis (yr)	48	48
Median age at start of chemotherapy (yr)	56	54
Median disease-free interval (yr)	1.8	1.6
Median time-interval between diagnosis and start of chemotherapy (yr)	4	3
Performance status at start of chemotherapy (%):		
grades 0, 1	64	72
grades 2, 3	23	20
grade 4	13	8

Table 2. Previous treatment

	No. of patients Group A ($n = 53$)	Group AV ($n = 54$)
Mastectomy for primary operable disease	45	48
Radiotherapy for primary inoperable disease	8	6
Ovarian ablation	16	17
Androgens, oestrogens or antioestrogens	33	27
Hypophysectomy	1	2
Corticosteroids	21	19

Table 3. Response to treatment

	No. of patients Group A ($n = 53$)	Group AV ($n = 54$)
Objective regression		
complete response (CR)	1	2
partial response (PR)	29	26
CR + PR	30 (57%)	28 (52%)
No change	9	12
Progressive disease	14	14

*Table 4. Objective responses at sites of involvement**

	Group A	Group AV
Breast	11/20 (55%)	9/12 (75%)
Lymph nodes	19/28 (68%)	21/31 (68%)
Skin	17/33 (52%)	19/31 (61%)
Lungs	7/22 (32%)	12/21 (57%)
Skeleton	5/32 (16%)	5/35 (14%)
Pleura	2/4	2/9
Liver	3/5	0/1

* Numerator = No. of responses at stated site; denominator = No. of patients with stated site involved at start of treatment.

Toxicity

The projected dose of drugs given to both groups was 78% for A and 75% for AV. There was a tendency to increased haematological toxicity in group AV with regard to total WBC and platelet count (Table 5). Vincristine-induced thrombocytosis occurred in 23 patients (43%), but it did not permit a higher dose of adriamycin to be given as leukopenia was the dose-limiting factor in those patients.

Adriamycin-related subjective toxicity was similar in both groups (Table 6). The projected dose of vincristine received was 60%. The main reason for vincristine having to be discontinued

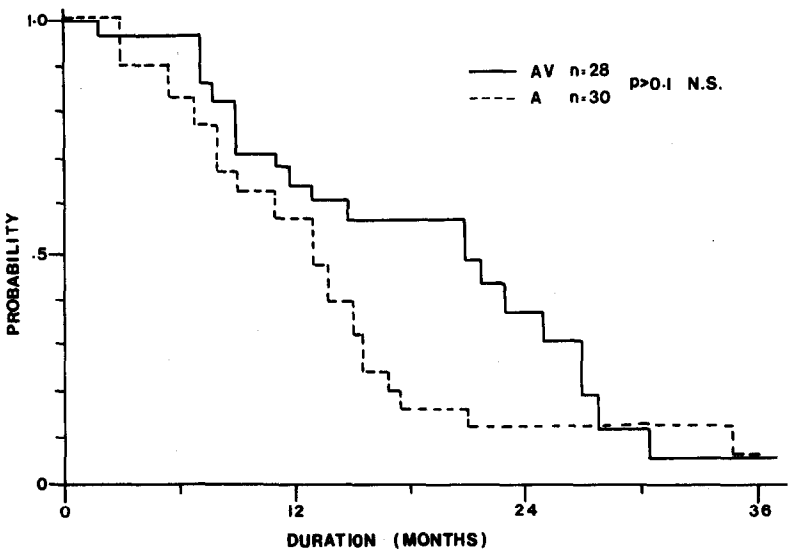

Fig. 1. Probability of survival of responders (CR + PR) in groups A and AV ($\chi^2 = 2.518$; P = 0.112).

Table 5. Haematological toxicity

		No. of patients (%)* Group A ($n = 53$)		Group AV ($n = 54$)	
White blood cell count					
grade 0	⩾4000/μl	28 (53%)		18 (33%)	
grade 1	2000–3999/μl	22 (42%)	47%	26 (48%)	67%
grade 2	<2000/μl	3 (5%)		10 (19%)	
Platelet count					
grade 0	⩾120,000/μl	50 (94%)		45 (83%)	
grade 1	70,000–199,000/μl	2 (4%)	6%	3 (6%)	17%
grade 2	⩽70,000/μl	1 (2%)		6 (11%)	

* Only the most severe episode of toxicity per patient is recorded.

Table 6. Toxicity related to adriamycin

	No. of patients (%) Group A ($n = 53$)	Group AV ($n = 54$)
Nausea and/or vomiting	42 (79%)	47 (87%)
Stomatitis	27 (51%)	27 (50%)
Diarrhoea	9 (17%)	8 (15%)
Anorexia	6 (11%)	4 (7%)
Alopecia	44 (83%)	47 (87%)
Drug-related death	1 (2%)	1 (2%)

was neurotoxicity, which affected 37 of 54 patients (69%).

One patient in each group died with drug-related toxicity, namely severe mucositis, septicaemia and pancytopenia.

DISCUSSION

Several clinical studies in advanced breast cancer have suggested that adriamycin in combination with vincristine could yield higher regression frequencies (52–66%) than adriamycin alone (40%) [5–9]. However, this has not been confirmed in this prospective controlled clinical trial, the response rate being 57% for adriamycin alone and 52% for adriamycin plus vincristine. The initial high response rate was not maintained in both treatment arms. In contrast to a study comparing adriamycin with cyclophosphamide with or without vincristine [8], we did not find that the addition of vincristine to adriamycin significantly prolonged the time to treatment failure (TTF) or survival. Subjective and haematological toxicities were similar in both groups, but 69% of the patients in group AV developed neurotoxicity. Vincristine-induced thrombocytosis (43%) did not allow higher doses of adriamycin to be given because the dose-limiting toxicity was leukopenia.

We conclude that adriamycin as a single agent induces a high frequency of response in advanced breast cancer. The addition of vincristine did not significantly affect response frequency, median time to failure or survival, and so it is not expedient to use these particular drugs in combination in this disease. It is appropriate for adriamycin alone to serve as a control arm in future prospective trials studying the use of this drug in combination with other drugs in the treatment of advanced breast cancer. Combining cytotoxic drugs may lead to more toxicity than the use of single agents, and the results of this trial demonstrate the importance of controlled trials in determining the precise contribution of individual drugs in combinations for advanced breast cancer.

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