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A Randomized, Prospective, Comparative, Multicentre Trial of a Single Combination Versus Alternating Combinations of Antitumour Drugs in Advanced Breast Cancer

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Abstract—*A prospective, multicentre trial was conducted in* 262 *patients with advanced breast cancer randomized to receive every* 3 *weeks either: (i) a single five-drug combination of adriamycin* (50 mg), *vincristine* (1.5 mg) *and* 5-*fluorouracil* (750 mg) *given intravenously; with methotrexate* (50 mg) *intramuscularly and chlorambucil* (10 mg) *orally all at time zero, followed by three further doses of chlorambucil* (10 mg) *at* 6-h *intervals, or (ii) one course of two alternating three-drug combinations consisting of regimen A—vincristine* (1.5 mg), *adriamycin* (70 mg) *and methotrexate* (50 mg) *and regimen B—*5-*fluorouracil* (750 mg) *and vindesine* (5 mg) *intravenously with cyclophosphamide* (50 mg) *orally at time zero, followed by three further doses of cyclophosphamide* (50 mg) *at* 6-h *intervals. Results show that overall response rates to chemotherapy were comparable in the two arms of this study being* 63% (83 *of* 131 *patients) for the single combination and* 64% (84 *of* 131 *patients) for the alternating combinations. Response rates according to menopausal status indicate no significant difference for the two arms of this study. However overall, combining all patients treated with either the single or the alternating combinations, post-menopausal patients had a significantly lower response rate* (57%) *compared with pre-menopausal patients* (76%), $P < 0.05$. *Overall serious side-effects were minimal and were similar in both treatment groups. Response durations and overall survival data, which are essentially similar for the two treatment groups, proved disappointing with a median response duration of only approx.* 6 *months and overall median survival only slightly in excess of* 1 *year. Alternative treatment approaches are needed to maintain the remissions initially achieved in metastatic breast cancer.*

INTRODUCTION

SINCE 1974 the Multicentre Cancer Chemotherapy Group (MCCG) in the U.K. has evaluated a series of combination chemotherapy regimens in advanced breast cancer. Their objective has been to identify protocols which not only have significant effect in advanced disease with acceptable toxicity, but also could be used for evaluation as potentially effective adjuvant chemotherapy.

In the first MCCG study [1] it was shown that a combination of cyclophosphamide, 5-fluorouracil, vincristine and methotrexate given over 5 days was superior to a single injection of these same drugs, with treatments on a monthly basis. However, a subsequent randomized study [2] showed that results comparable to those achieved using the 5-day protocol could be obtained with a 2-day regimen (days 1 and 8). This 2-day regimen was then used in an adjuvant study and 5-year results have recently been published [3]. Further improvement in response rates in advanced disease was next obtained by adding adriamycin to the 2-day protocol [4]. In an attempt to reduce the number of times a patient had to attend for hospital treatment the 2-day regimen including adriamycin, repeated every 4 weeks, was next compared with a 30-h regimen, including oral chlorambucil and methotrexate at 6-h intervals for four doses, given every 3 weeks.

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Table 1. *Details of chemotherapy protocols*

Single combination		
Adriamycin	50 mg i.v.	
Vincristine	1.5 mg i.v.	
5-Fluorouracil	750 mg i.v.	
Methotrexate	50 mg i.m.	
Chlorambucil	10 mg orally—	four doses at 6-h intervals, the first dose at time of i.v. therapy
Alternating combinations		
Regimen A		
Vincristine	1.5 mg i.v.	
Adriamycin	70 mg i.v.	
Methotrexate	50 mg i.m.	
Regimen B		
5-Fluorouracil	750 mg i.v.	
Vindesine	5 mg i.v.	
Cyclophosphamide	50 mg orally—	four doses at 6-h intervals, the first dose at time of i.v. therapy.

Comparable response rates of approx. 70% were achieved with both protocols. However, the durations of response were short-lived and at least 50% of patients had relapsed within 1 year.

In this latest study designed in 1978, our main objective was to attempt to maintain the remissions initially achieved. Therefore we (i) incorporated the newer Vinca alkaloid vindesine into the protocol, since in initial Phase II clinical trials it has been shown, as a single agent, to have some activity in advanced breast cancer [5, 6], and (ii) utilized two alternating three-drug regimens, based on certain cell kinetic concepts, reviewed by Hill [7]. In particular we attempted to test one of the implications of a hypothesis proposed by Norton and Simon [8] as part of their 'late intensification' model, namely that intensive, alternating sequences of different drugs in full doses might produce better survival times than using one particular combination of many agents in reduced doses.

The results obtained in this randomized, prospective trial comparing these two alternating drug combinations with a single combination of adriamycin, vincristine, 5-fluorouracil, methotrexate and chlorambucil with the latter drug given over 24-h (four doses at 6-h intervals), are presented here. This study demonstrates that it is feasible to carry out a multicentre chemotherapy trial, involving non-specialist centres, in advanced breast cancer and that high initial response rate (approx. 60–70%) can be reliably achieved with minimal associated side-effects. Unfortunately the magnitude of the response resulting from this treatment failed to translate into prolonged durations of response or significant extensions of survival in the majority of patients.

PATIENTS AND METHODS

The eligibility criteria for entry into this study were as follows: (i) patients should be aged less than 70 years, (ii) patients should have progressive, locally advanced and/or metastatic disease beyond cure by standard surgical or radiotherapeutic techniques, (iii) patients should not have received adjuvant chemotherapy within the previous 3 months, and (iv) patients with cardiac disease or impaired renal function should be excluded. Two hundred and sixty-two patients were judged eligible for analysis in this trial, with 131 patients in each treatment arm. The first patient was treated in July 1978. The study was closed in December 1983, with the last course of chemotherapy being administered in July 1984. The chemotherapy protocols used are listed in Table 1. Fixed rather than size-adjusted dosage was used, based on results from our previous studies [1–4] and kinetic and pharmacologic considerations [7]. Treatment cycles were repeated every 3 weeks. In the few instances (< 10%) of bone marrow depression treatment was postponed for 1 week, but no dose reductions were employed. The dose of vincristine or vindesine was reduced in the small number of patients (< 10%) experiencing paresthesiae. The total dose of adriamycin never exceeded 550 mg/m^2.

Three physiological categories of menopausal status were recognized: pre-menopausal—a menstrual period had occurred within the previous 6 months; peri-menopausal—last period occurred 6 months to 5 years previously; post-menopausal—last period occurred > 5 years ago. Response to chemotherapy was assessed using the UICC criteria [9], except that patients were classified into two groups only: responders—which

Table 2. Patient data by treatment category as determined at entry into the study

	Single combination	Alternating combinations
Age		
< 40	14 (11%)	8 (6%)
40–49	36 (27%)	40 (31%)
50–59	53 (41%)	51 (39%)
60–68	28 (21%)	32 (24%)
Performance status		
Normal activity	58 (44%)	54 (41%)
Normal activity with symptoms	43 (33%)	37 (28%)
Reduced activity, largely housebound	25 (19%)	34 (26%)
Bedridden	3 (2%)	6 (5%)
Not known	2 (2%)	0
Sites of involvement		
Single site	40 (30%)	44 (34%)
Two sites	61 (47%)	53 (40%)
Three or more sites	30 (23%)	34 (26%)
Localized	15 (11%)	12 (9%)
Lymphatic	34 (26%)	23 (17%)
Skeletal	18 (14%)	18 (14%)
Visceral	19 (15%)	17 (13%)
Lymphatic and skeletal	12 (9%)	13 (10%)
Skeletal and visceral	19 (15%)	24 (18%)
Visceral and lymphatic	8 (6%)	14 (11%)
Lymphatic, skeletal and visceral	6 (4%)	10 (8%)
Menopausal status		
Pre-menopausal	27 (21%)	27 (21%)
Peri-menopausal	20 (15%)	26 (20%)
Post-menopausal	84 (64%)	78 (59%)
Prior local treatment		
None	19 (14%)	15 (11%)
Surgery	18 (14%)	21 (16%)
Radiotherapy	23 (18%)	23 (18%)
Surgery and radiotherapy	71 (54%)	72 (55%)
Prior systemic treatment		
None	59 (45%)	58 (44%)
Endocrine manipulation	61 (46%)	59 (45%)
Adjuvant chemotherapy	6 (5%)	9 (7%)
Chemotherapy and tamoxifen	5 (4%)	4 (3%)
Chemotherapy for advanced disease	0	1 (1%)

included the UICC category of partial responders (PR) only, since we considered that all responses in this study were partial, and non-responders—which include the UICC categories of both no change (NC) and progressive disease (PD).

Initial response rates were compared using the chi-squared test. Survival and response durations were calculated by a life-table method and compared using a log-rank test.

RESULTS

Patient characteristics

The balance achieved by randomization is apparent from the data listed in Table 2 showing that the distributions for most of the factors determined at entry into the study were very similar for each of the two treatment groups.

Effects of chemotherapy

The median time on therapy was similar for both groups being 5.6 months for the single combination and 6.5 months for the alternating combinations. Overall response rates to chemotherapy were comparable in the two arms of the study being 63% for the single combination protocol and 64% for the alternating combinations. Analysis of these response rates according to menopausal status, provided in Table 3, indicates no significant difference between the two protocols. However, analysing all the patients treated in this study (i.e. irrespective of whether they received the single or the alternating combi-

Table 3. Chemotherapy response rates

	Single combination			Alternating combinations		
	Responders*	Non-responders†	%	Responders	Non-responders	%
All patients	83	48	63%	84	47	64%
Pre-menopausal patients	21	6	78%	20	7	74%
Peri-menopausal patients	13	7	65%	20	6	77%
Post-menopausal patients	49	35	58%	44	34	56%

*Includes UICC category of partial responders only.
†Includes UICC categories of no change *and* progressive disease.

Table 4. Incidence of side-effects in patients receiving chemotherapy

		Single combination		Alternating combinations	
Side-effects	at:	1 month*	4 months*	1 month*	4 months*
Haematologic:					
haemoglobin (< 10 g)		3%	6%	2%	2%
white blood cell count (< 2000 per mm^3)		2%	7%	6%	3%
platelet count (< 100,000 per mm^3)		1%	2%	2%	2%
Nausea—definite		64%	65%	51%	57%
(severe)		(27%)	(30%)	(15%)	(18%)
Vomiting—definite		41%	49%	28%	25%
(severe)		(17%)	(19%)	(13%)	(8%)
Stomatitis		5%	4%	7%	7%
Diarrhoea		4%	1%	3%	4%
Constipation		4%	4%	6%	2%
Neurological—definite		7%	9%	4%	5%
(severe)		(2%)	(1%)	(1%)	(3%)
Alopecia—slight		30%	13%	32%	9%
—marked		24%	41%	33%	34%
—total		14%	26%	10%	35%
—regrowth		—	10%	—	16%

*Side-effects recorded 1 and 4 months after commencing chemotherapy.

nations), post-menopausal patients had a significantly lower response rate to chemotherapy compared with pre-menopausal patients ($P < 0.05$).

Toxicities

Side effects were recorded on a monthly basis and the significant toxicities are listed in Table 4, which provides details after 1 month and 4 months of treatment. Overall serious side-effects were minimal and were similar in both treatment groups. Significant alopecia occurred in approx. 70% of patients treated, whilst nausea and vomiting were the most troublesome symptoms occurring in most patients. The overall impression from participating clinicians was that the alternating combinations were better tolerated than the single combination protocol, with fewer refusals (2 vs. 7) being reported.

Durations of response and survival data

Response durations and overall survival data are plotted in Fig. 1, and these are essentially similar for the two treatment groups: $P = 0.32$ for durations of response and $P = 0.62$ for overall survival. Following evidence of disease progression approx. 50% of patients in each group received a variety of further treatments (see Table 5), which however did not appear to have any significant impact on overall survival figures. The median durations of response and survival figures, analysed according to meno-

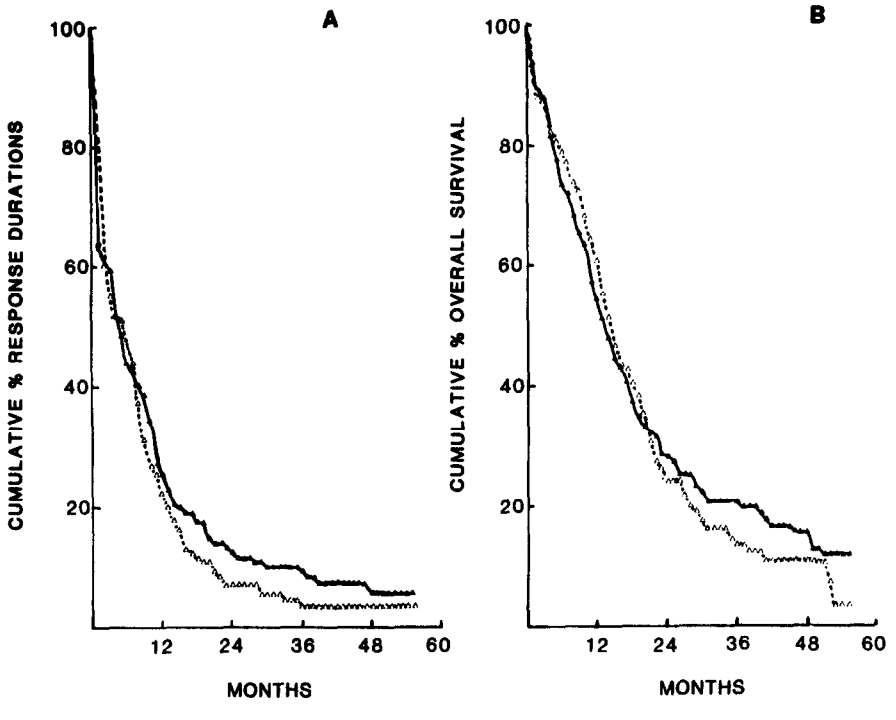

Fig. 1. *A. Response durations in all patients. B. Overall survival of all patients:* —— *single combination;* ----*alternating combinations.*

Table 5. *Treatment following failure on chemotherapy*

Treatment	Single combination	Alternating combinations
Hormones or endocrine manipulation	29	31
Radiotherapy	9	14
Radiotherapy + tamoxifen	3	5
Alternative chemotherapy	15	11
Radiotherapy + alternative chemotherapy	1	1
Steroids (prednisolone or durabolin)	2	5

pausal status, are listed in Table 6 and illustrate the disappointing results of this study, with a median response duration of approx. 6 months and overall survival only slightly in excess of 1 year.

With the exception of four patients, all patients who have died did so following a period of disease progression. The exceptions included two patients who received the single combination, one died from leukaemia at 37 months whilst in remission and the second died as a result of a CVA at 4 months. The other two patients were treated with the alternating chemotherapy and one died in remission following a CVA at 21 months, whilst the other died at 12 months from respiratory failure, not attributed to her disease.

DISCUSSION

In this study initiated in 1978 we incorporated a newer antitumour agent, vindesine, with initial reported activity in advanced breast cancer [5, 6], into a multi-drug combination and evaluated the benefits of using two alternating drug combinations. Unfortunately the results indicate that response rates and overall survival were not significantly improved by either of these strategies. Our data are comparable with other published studies describing effects in advanced breast cancer of most forms of first line combination chemotherapy, yielding response rates ranging from 45–70%, with median durations of response ranging between 7 and 13 months and overall median survival figures between 12 and 24 months, as reviewed by Bonadonna and Valagussa [10] and more recently by Paridaens [11]. However, these present results were obtained with minimal associated toxicities. In particular haematologic toxicity was significantly lower than that reported in a number of other advanced breast cancer studies [12–14]. The side-effects recorded here were comparable in the two arms of the study, although participating clinicians considered that the alternating combinations were better tolerated than the single combination.

In the light of more recent experimental and clinical data [15–19] these essentially negative results are perhaps not surprising. They do, however, serve to emphasize the essential requirements for careful attention to detail in the design of future

Table 6. Median response durations and survival figures

	Response durations (months)		Overall survival (months)	
	Single combination	Alternating combinations	Single combinations	Alternating combinations
All patients	5	6	14	15
Pre-menopausal	8	8	18	18
Peri-menopausal	8	10	16	20
Post-menopausal	4	3	13	14

studies aimed at improving the treatment of this disease: for example, the quantitative requirements, emphasized recently by Goldie *et al.* [16], for alternating chemotherapy regimens and the importance of delivered dose intensity [18]. Considerable interest has been focused recently on the idea of using alternating chemotherapy protocols. This has arisen from the introduction of a somatic mutation model for drug resistance proposed by Goldie and Coldman [15]. One of their predictions is that 'when large numbers of cytotoxic agents are available for therapy, then alternating non-cross-resistant treatment at every cycle will be superior to using the same treatment arms in a sequential fashion' [16, 17]. However, this model requires that the two treatment arms are not only cross-resistant but also equally effective in their own right. In our present study design it is likely that regimen A, containing adriamycin, is superior to regimen B and we have not determined whether or not the two regimens are non-cross-resistant. Likewise, the use of fixed dosage schedules, though making it feasible for the chemotherapy to be administered safely, even in non-specialized centres, must be considered as a factor likely to compromise seriously the effectiveness of the treatment.

In terms of dose intensity the recent publications by Hrynuik and colleagues [18, 19] have clearly indicated a relationship not only between delivered dose intensity and remission rate, but also between median survival and remission rate. If we express the dose intensities of cyclophosphamide, methotrexate and 5-fluorouracil, as included in our regimens, as a fraction of the dose intensities of these drugs in Cooper's modification of his original regimen [20] it can be seen that in the single combination the relative dose intensities were 0.40 for methotrexate and 0.35 for 5-fluorouracil, whilst in the alternating protocols the ratios were even lower being 0.04 for cyclophosphamide, 0.20 for methotrexate and 0.17 for 5-fluorouracil. Even with adriamycin, considered the most active single agent, compared with the dosage in the Bull and Tormey protocol cited by Hrynuik and Bush [18], the dose intensity factor is only 0.74 for the single combination and 0.52 for the alternating regimens.

Clearly, therefore, one implication from these studies is that future trials should be designed so as to maximize the dose intensity of individual agents. Although attempts to increase the complete remission rate by increased drug dosage will undoubtedly mean increased toxicities, a few positive results have been reported in non-randomized studies using such high-dose therapy [14, 21, 22]. Alternative strategies for attempting to decrease significantly the observed mortality rate in advanced breast cancer might include (i) a comparison of different drug schedules, (ii) establishing the value of adding to existing drug combinations new agents identified in Phase II trials as having activity in advanced breast cancer, for example novantrone [23, 24] and epirubicin [25, 26] and (iii) evaluating concomitant administration of antitumour and hormonal drugs. Several such studies have claimed higher response rates in excess of 70%, however significant survival benefit for patients treated with this combined modality remains to be demonstrated [27, 28]. In attempting to test each of these approaches it appears critical that the dose intensity of the most active drugs should be equivalent in each treatment arm [18].

The essentially negative results of this study make us aware, at least retrospectively, of the various problems associated with our regimens. Improved awareness of these critical factors should facilitate the design of improved protocols aimed at achieving not only increased response rates but improved survival in advanced breast cancer.

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