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Combined Chemotherapy and Radiotherapy for Locally Advanced Breast Cancer

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Abstract—*To test the feasibility of combining radiotherapy and chemotherapy as the primary management of locally advanced breast cancer,* 24 *patients were allocated to receive either* 4 *courses of adriamycin and vincristine (AV) followed by radiotherapy, followed by* 8 *courses of cyclophosphamide, methotrexate and* 5*-florouracil (CMF) (group A) or radiotherapy followed by* 4 *courses of AV followed by* 8 *courses of CMF (group B). The objective regression rate after AV and radiotherapy was* 10/12 (83%) *in group A and* 11/12 (92%) *in group B, but the subsequent relapse rate was high being* 6/12 (50%) *in group A and* 7/12 (58%) *in group B. The pattern of relapse, duration of objective regressions and survival in groups A and B were the same. No serious adverse side effects arose from combining chemotherapy and radiotherapy in either group. In a retrospective comparison of groups A and B with patients treated previously by radiotherapy alone, the median duration of response in this series of* 33 months *was significantly longer than in patients treated by radiotherapy alone* (10.5 months); $P \leq 0.001$. *Although the survival experience of the combined groups A and B (median* 36 months) *was higher than that in the previous series* (25 months) *this difference is not statistically significant. While these retrospective comparisons give rise to optimism that combining radiotherapy and chemotherapy may be helpful in the treatment of locally advanced breast cancer, prospective randomized controlled trials are now necessary to determine whether a true improvement in results can be achieved by this approach.*

INTRODUCTION

LOCALLY advanced inoperable breast cancer is treated usually by radiotherapy, but survival is poor and most patients develop distant metastases [1]. For this reason interest has developed in combining chemotherapy with local treatment in the primary management of the disease at this stage with the intention of suppressing the subclinical distant metastatic disease responsible for relapse in most patients treated by radiotherapy alone. We report here a pilot study which was designed to investigate the feasibility of combining chemotherapy with radiotherapy. This is not a prospective radomised clinical trial, but the results are compared with previous experience at this hospital using radiotherapy alone [1].

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MATERIALS AND METHODS

Patients were eligible for this study if, after full physical examination, chest radiography and radiographic bone survey, they had locally advanced inoperable disease without evidence of distant metastases. Features of locally advanced disease indicating inoperability were infiltration of the overlying skin, satellite skin nodules over the affected breast, peau d'orange, attachment to deep structures, fixation of axillary lymph nodes, and/or involvement of supraclavicular lymph nodes. On the TNM classification [2], these cases would be classified as either any T,N2,3,M0 or T3,4, any N,M0 (stage 3) that were suitable for standard radical radiotherapy techniques. Large primary tumours which did not have the above features of inoperability (i.e., T3 N0, 1 M0, also stage 3) were considered operable and not eligible for this study.

Patients were allocated alternately, not randomly, to one of 2 treatment groups (A or

B) in this study to test the feasibility of two combinations of radiotherapy with chemotherapy (Fig. 1).

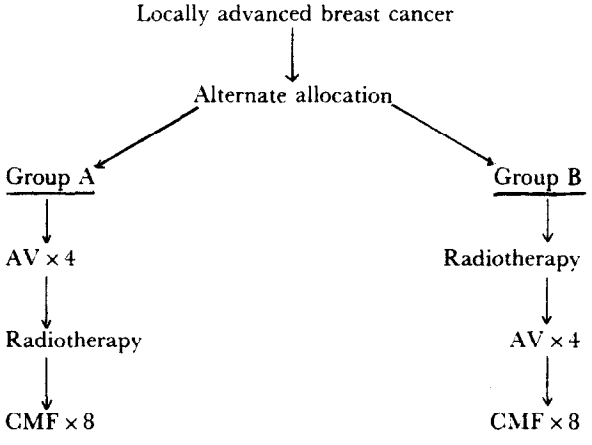

Fig. 1. Scheme for feasibility study of combining radiotherapy and chemotherapy in the primary treatment of locally advanced breast cancer. A—Adriamycin; V—Vincristine; C—Cyclophosphamide; M—Methotrexate; F—5-Fluorouracil. See text for doses and schedules.

Group A

Patients were treated initially with 4 courses of adriamycin, 70 mg/m^2 (,aximum 120 mg) (60 mg/m^2 in patients aged $\geqslant$60 yr) i.v., on day 1 and vincristine, 1.4 mg/m^2 (maximum 2 mg) i.v. on days 1 and 8 (AV). The cycle was repeated 3-weekly for 4 courses. Starting three weeks after completion of this chemotherapy, patients received megavoltage radiotherapy to the breast and ipsilateral internal mammary, axillary and supraclavicular lymph nodes concurrently to 4000 rad given in 10 fractions over 4 weeks, after which, residual palpable disease was given a further 300 rad × 3–4 in daily fractions by a direct field with 250 kV X-rays or ^{137}Caesium gamma-rays. After radiotherapy patients then received 8 cycles of cyclophosphamide, 100 mg/m^2 (maximum 150 mg) orally, on days 1–14, methotrexate 30 mg/m^2 (maximum 50 mg) (patients $\geqslant$60 yr 20 mg/m^2; maximum 40 mg) i.v., on days 1 and 8 and 5-fluorouracil, 600 mg/m^2 (patients $\geqslant$60 yr 400 mg/m^2) i.v., on days 1 and 8, the cycle being repeated at 4-weekly intervals for 8 courses (CMF). CMF was started three weeks after the completion of radiotherapy.

Group B

These patients started treatment with radiotherapy as for group A and then received 4 cycles of adriamycin and vincristine followed by 8 cycles of cyclophosphamide, methotrexate and 5-fluorouracil in the doses and schedule for group A.

Full doses of all cytotoxic drugs were given provided the total white blood cell count was $\geqslant$4000/μl and the platelet count $\geqslant$120,000/μl. For total white cell counts between 2000 and 3999/μl or platelet counts between 70,000 and 99,999 μl, only 50% doses were given; with counts below these lower limits drugs were omitted.

Patients were assessed clinically on day 1 of each cycle of chemotherapy, and before and after radiotherapy. When the whole course of treatment had been completed, follow-up continued at 3-monthly intervals.

Response to treatment was assessed using the system recommended by the U.I.C.C. [3]. Briefly, complete response means a complete disappearance of all visible and palable tumour confirmed by 2 observations not less than 4 weeks apart. Partial response indicates a reduction in size of 50% or more of the sum of the products of the diameters of each individual tumour mass present. No change infers that there was a reduction in tumour size of less than 50% or an increase in tumour size of less than 25%. Progressive disease was deemed to occur when tumour size increased by 25% or more at the first assessment after starting treatment and/or the appearance of new lesions. Duration of tumour regression is taken from the time of starting treatment to the date of the first sign indicating progressive disease. In cases of complete or partial response or no change the time of relapse was taken as the date on which measurements were recorded as being 25% greater than the minimum size recorded previously or the date of appearance of new lesions, whichever occurred first.

RESULTS

A total of 24 patients were included in this study. The characteristics of the patients studied are shown in Table 1. The two groups are similar except that, by chance, there is a preponderance of early postmenopausal women in group A. The characteristics of the tumours are listed in Table 2.

All patients in this pilot study have completed the precribed course of treatment and the responses are detailed in Table 3. For both groups, the objective regression rate (CR + PR), after the combined AV and radiotherapy, was high, 10/12 (83%) in group A and 11/12 (92%) in group B. One patient

Table 1. *Patient characteristics*

	No. of patients	
	Group A	Group B
Total	12	12
Age		
20 yr-	2	1
40 yr-	9	8
60 years	1	3
Menopausal status		
Pre- (and < 1 yr post)	4	7
Post (1–5 yr)	7	1
Post (≥5 yr)	1	4
Duration symptoms (months)		
Median	3	3
Range	<1–144	<1–12

Table 2. *Tumour characteristics*

	No. of patients	
	Group A	Group B
Total	12	12
Maximum diameter		
<5 cm	0	0
≥5–<10 cm	7	7
≥10 cm	5	4
diffuse	0	1
Skin		
—Attachment	12	12
—Involvement	8	12
Deep fixation	2	2
Nodes involved		
Ipsilateral axilla (free)	7	7
Ipsilateral axilla (attached)	1	1
Ipsilateral supraclavicular fosa	4	1
Lymphoedema of ipsilateral arm	1	0
TNM category		
T3a	4	0
T3b	0	0
T4b	8	12
N0	2	4
N1	4	6
N2	1	1
N3	5	1

in group B relapsed during radiotherapy with distant metastases, but responded subsequently to AV. Despite the initial high response rates, 4 patients relapsed whilst on CMF (3 in group A and 1 in group B). During follow-up, after completion of treatment, of up to 40 months at the time of analysis, further relapses occurred, bringing the total number of patients with progressive disease to 6/12 (50%) in group A and 7/12 (58%) in group B.

The pattern of relapse is shown in Table 4 and is similar in both groups. The site of first relapse was local in the irradiated volume in 3 patients in group A and 5 in group B, and distant in 3 and 4 patients in the respective groups; 2 patients in group B relapsed at both local and distant sites simultaneously.

The duration of objective regressions (CR + PR) in both groups was the same (33 months). This is significantly longer than in a previous series of patients treated by rad-

*Table 3. Response to treatment**

Group A ($n=12$)	Response	After AV	After radiotherapy	After CMF	Subsequent PD	Total PD
	CR	2	5	8		
	PR	4	5	1		
	NC	6	2	0		
	PD	0	0	3	3	6
Group B ($n=12$)	Response	After radiotherapy	After AV	After CMF	Subsequent PD	Total PD
	CR	1	5	9		
	PR	7	6	2		
	NC	3	1	0		
	PD	1	0	1	6	7

*The figures relate to the number of patients in each response category at each stage of treatment
CR = Complete response.
PR = Partial response.
NC = No change.
PD = Progressive disease.

Table 4. Sites of relapse

	No. of patients Group A	Group B
Breast	2	3
Skin	4	3
Lymph nodes	2	2
Skeleton	4	3
Pleura	0	2
Lung	2	1
Pericardial	0	1
Liver	3	4
Acites	0	1
Brain	0	1

iotherapy alone, when the median duration of response was only 10.5 months ($P<0.001$, Fig. 2).

The survival experience of groups A and B, analysed by the log rank method [4], is the same (median 36 months), but when compared to the previous series [1] (Fig. 3), is not significantly longer than those patients treated by radiotherapy alone (25 months).

Cytotoxic drug adminstration and toxicity

The projected doses of cytotoxic drugs administered were high, but modifications in

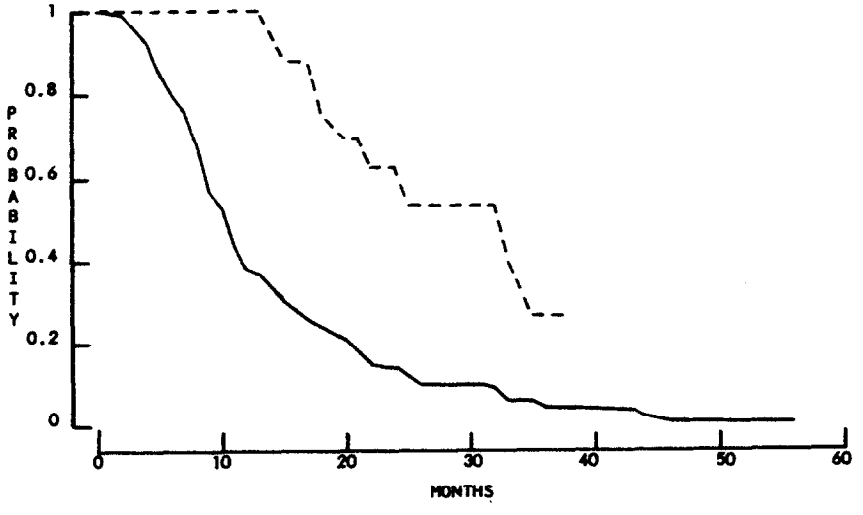

Fig. 2. Duration of response of objective regressions (complete + partial responses). (- - -) Patients treated by combined radiotherapy and chemotherapy (n = 20). (—) *Patients treated by radiotherapy alone* (n = 105), $P<0.001$.

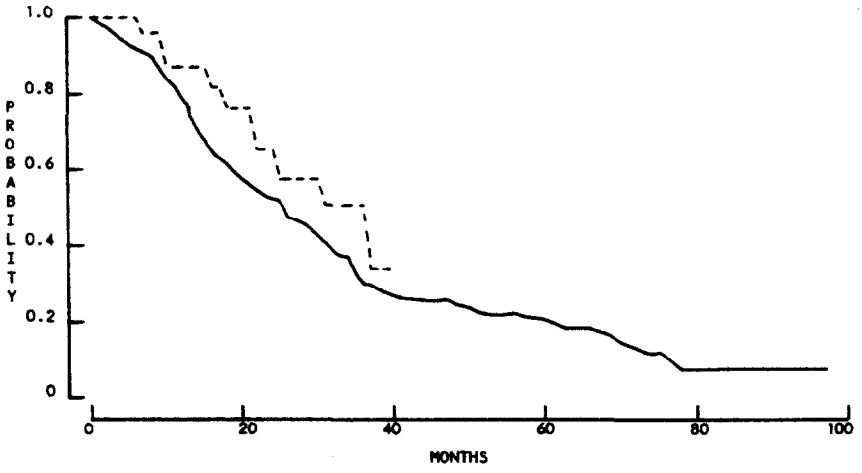

Fig. 3. Survival. (---) *Patients treated by combined radiotherapy and chemotherapy* (n=24). (—) *Patients treated by radiotherapy alone* ($n=184$), P=0.2

accordance with falls in blood count and other toxicity resulted in patients in group B receiving lower doses of all drugs than those in group A (Table 5) but this was significantly different only for adriamycin. These results indicate that prior radiotherapy led to a decreased tolerance of the bone marrow to chemotherapy. Haematological and other toxicity are detailed in Tables 6 and 7, respectively. In general, toxicity was not severe, nor were there adverse effects from combining radiotherapy and chemotherapy, such as cardiotoxicity or skin reactions.

Table 5. Cytotoxic drug administration

	Mean total dose given*		
	Group A	Group B	Difference
Adriamycin	95%	83%	P<0.05
Vincristine	83%	71%	N.S.
Cuclophosphamide	74%	59%	N.S.
Methotrexate	82%	75%	N.S.
5-Fluorouracil	81%	75%	N.S

*Mean total dosage received by patients, after reductions based on bone-marrow suppression or other toxicity, expressed as a percentage of the calculated total doses that would have been given if these reductions had not been necessary.
N.S.—Not Significant.

Table 6. Haematological toxicity

	No. of patients*	
	Group A	Group B
White blood cells ($\times 10^3/\mu l$)		
2–4	9	10
<2	0	1
Platelets ($\times 10^4/\mu l$)		
8–12	5	3
<8	1	3
	Nadir counts	
White blood cells ($\times 10^3/\mu l$)		
Mean	3.3	2.6
Range	2.6–5.1	1.0–3.7
Platelets ($\times 10^4/\mu l$)		
Mean	12.4	10.5
Range	5.3–17.5	1.6–17.5

*No. of patients who experienced the toxicity listed on one or more occasions.

Table 7. Cytotoxic drug toxicity

	No. of patients* Group A	Group B
Total	12	12
AV		
Nausea/vomiting	12	8
Stomatitis	3	4
Alopecia	12	12
Cardiomyopathy	0	0
Thrombocytosis	3	3
Neurotoxicity	7	8
Constipation	3	1
CMF		
Nausea/vomiting	9	6
Stomatitis	2	2
Cystitis	0	0

*No. of patients who experienced the toxicity listed on one or more occasions.

Complications of radiotherapy

There were no unusual side effects, either immediate or delayed, with the dose of radiation given. The most common problem was moist desquamation or ulceration of the treated axilla which resolved with standard management. Brawny induration of the pectoralis major muscle was the commonest delayed effect, but symptomatic radiation changes in the underlying lung (radiation pneumonitis or fibrosis) were seen in only one patient to a minor extent.

DISCUSSION

The results of this study show it is feasibile to combine radiotherapy and chemotherapy in the primary management of locally advanced inoperable breast cancer. In the doses and schedules used here, the combined treatments did not lead to adverse toxicity. In a retrospective comparison, the objective regression rate from combined radiotherapy and chemotherapy appears to be higher and lasts longer than with radiotherapy alone, but survival was not significantly improved. These results are partly in agreement with those of De Lena *et al.* [5], who also showed a significantly improved survival on combined treatment. However, in both studies, the radiotherapy schedules given to the study group are different from those received by the historical controls. While these retrospective comparisons give rise to optimism that combining radiotherapy and chemotherapy may be helpful in the treatment of locally advanced breast cancer, prospective controlled randomised trials, in which the radiotherapy is standardised, are now necessary to determine whether a true improvement can be achieved by this approach.

REFERENCES

1. R. D. Rubens, P. Armitage, P. J. Winter, D. Tong and J. L. Hayward. Prognosis in inoperable stage 3 carcinoma of the breast. *Europ. J. Cancer* **13,** 805 (1977).
2. Union Internationale Contre le Cancer, TNM Classification of Malignant Tumours, 3rd edition. *Breast* p. 47 (Edited by M. H. Harmer) Geneva (1978).
3. J. L. Hayward, R. D. Rubens, P. P. Carbone, J.-C. Kumaoka and S. Segaloff, Assessment of response to therapy in advanced breast cancer. *Brit. J. Cancer* **35,** 292 (1977).
4. R. Peto, M. C. Pike, P. Armitage, N. E. Breslow, D. R. Cox, S. V. Howard, N. Mantel, K. McPherson, J. Peto and P. G. Smith, Design and analysis of randomised clinical trials requiring prolonged observations of each patient. 2. Analysis and examples. *Brit. J. Cancer* **35,** 1 (1977).
5. M. de Lena, R. Zucali, G. Viganotti, P. Valagussa and G. Bonadonna, Combined chemotherapy–radiotherapy approach in locally advanced (T_{3b}–T_4) breast cancer. *Cancer Chemother. Pharmacol.* **1,** 53 (1978).