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Original Paper

Locally Advanced Breast Cancer: Early Results of a Randomised Trial of Multimodal Therapy Versus Initial Hormone Therapy

P.C. Willsher,[1] J.F.R. Robertson,[1] S.Y. Chan,[2] L. Jackson[1] and R.W. Blamey[1]

[1]Professorial Department of Surgery, City Hospital, Nottingham; and [2]Department of Clinical Oncology, City Hospital, Nottingham, U.K.

The aim of this study was to investigate initial treatment of locally advanced breast cancer. Patients were randomised to "multimodal" therapy (pre-operative chemotherapy, Patey mastectomy, flap irradiation and adjuvant hormone therapy) ($n = 55$), or initial "hormone" therapy ($n = 53$) with further therapy upon tumour progression. The objective response to chemotherapy was 57% (31/54) after four cycles. Of patients on hormone therapy, 36% (19/53) had an objective response and 32% (17/53) disease stasis at a 6 month assessment. At a median 30 months follow-up, there was no notable difference in development of metastases or survival: only 6 patients have uncontrolled loco-regional relapse (4 "hormonal", 2 "multimodal"). The number of treatments per patient required for this loco-regional control was lower in the "hormone" group (mean 2.13 versus 4.20 in the "multimodal" group). This small study has shown that the use of consecutive therapies, with the aim of tumour control, does not appear to compromise outcome in comparison with initial "multimodal" therapy. Adopting such a policy may allow some patients to avoid unnecessary treatments.

Key words: breast carcinoma, Stage III, chemotherapy, hormone therapy

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INTRODUCTION

THE MANAGEMENT of locally advanced breast cancer has changed over the past two decades. Following recognition that local therapy alone was associated with high local recurrence rates and poor survival outcome, multimodal therapy has become the more widely used approach [1]. While this approach may improve initial local control, this has not been established and neither has a survival benefit been demonstrated [2, 3]. Each of chemotherapy, radiotherapy and surgery has associated morbidity, and it is unclear whether all patients with locally advanced breast cancer benefit from initial treatment with all these therapies.

In the early 1980s, the most usual initial treatment of locally advanced breast cancer was radiotherapy, but 5-year survival in patients with this condition was poor due to the inevitable presence of occult metastatic spread at diagnosis. We proposed a different approach using initial hormone therapy from which local control would be accompanied by an effect on metastasis [4]. A randomised trial was carried out comparing initial treatment by radiotherapy with initial treatment with tamoxifen followed by treatment cross-over on treatment failure [5]. This trial showed no disadvantage to starting with tamoxifen, which we have termed "minimal" therapy. However, ultimate local control was poor in both arms with 20% of patients dying with uncontrolled local disease. We, therefore, decided to adopt a more aggressive approach using multimodal therapy: primary chemotherapy, radical surgery, radiotherapy and hormone therapy (which we termed "maximal" treatment). This was compared with the initial hormone approach in the earlier trial (above). In this second trial, we have therefore compared a "maximal" versus "minimal" approach to management. We are particularly interested in the effect on local control.

The role of radiotherapy in local control has been well documented. As long ago as 1895, Halsted [6] showed that

Correspondence to P. C. Willsher.
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radical surgery dramatically improved local control as it is likely that many of the tumours he operated on were locally advanced. Local recurrence rates have been noted to be improved by systemic adjuvant therapies and the case for pre-operative therapy has been advanced [7]. However, there are potential advantages of the "minimal" approach: (1) the sequential use of treatment allows therapy to be tailored to the specific clinical problem that each individual patient presents, which may allow some patients to avoid a therapy they would automatically receive with the "maximal" approach; (2) patients receive a systemic therapy with potential for control of both local and occult metastatic disease. When the local lesion remains untouched by local treatments to the breast, it acts as a marker of response to therapy, and patients receiving hormone therapy can be maintained on that therapy so long as the response is seen to continue. This paper reports the early results of a randomised trial comparing initial "maximal" multimodal therapy with initial "minimal" hormone therapy alone in 108 patients with locally advanced breast cancer.

PATIENTS AND METHODS

Patient accrual

Patients with locally advanced breast cancer presenting to the City Hospital Breast Unit between January 1989 and December 1994, who were considered fit to have chemotherapy and surgery were invited to enter the study. Breast cancer was considered locally advanced if the diameter of the primary tumour was greater than 5 cm or if there was gross skin involvement or chest wall fixity, or if there was grossly fixed axillary nodal disease at diagnosis of the primary tumour. Prior to treatment, all patients had the diagnosis confirmed by Tru-cut biopsy or cytology. Menopausal status at presentation was determined by luteinizing hormone and follicle stimulation hormone levels in patients less than 55 years of age who had undergone hysterectomy or were within 2 years of their last menstrual period. Patient assessment included measurement of local disease, and overt metastases were excluded by a limited radiographic skeletal survey. Full blood count, urea and electrolytes and liver function tests were also performed. Isotope bone scans and liver ultrasound were only performed if clinically indicated or when there was an abnormality on liver function test. Patients were treated in a single clinic and reviewed every 2 months for six months and every three months thereafter.

Local disease was measured in two dimensions using calipers and response categorised according to UICC criteria [8], using the bidimensional product. Objective response includes complete response with resolution of the clinical lesion and partial response with greater than 50% reduction in the bidimensional product, static disease was defined as where the product decreased by less than 50% and increased by less than 25%, and progressive disease where the bidimensional product increased by more than 25% or a new lesion developed. Limited skeletal surveys were repeated at six monthly intervals. As recommended by the British Breast Group, patients were only classified as showing response or static disease after 6 months of treatment [9]. Since it has previously been demonstrated that patients with static disease for 6 months on endocrine therapy have a similar prognosis to patients who have a partial response [10, 11], for the purpose of analysis, objective response and static disease groups were combined.

Trial protocol

Minimal arm. 53 patients were randomised to receive initial hormone therapy. All were given tamoxifen 20 mg daily and 7 premenopausal women also received goserelin 3.6 mg by monthly s.c. injection. Assessment of initial response to hormone therapy was performed after 6 months of treatment. Patients in this arm of the trial were continued on their initial hormone therapy until they showed disease progression. Subsequent therapy for loco-regional control was not dictated by protocol, but the most appropriate treatment was decided by consultation between the clinician and patient.

Maximal arm. 55 patients were randomised to initial multimodal therapy. These patients were first given "MMM" pre-operative chemotherapy over three months (mitoxantrone 7 mg/m^2 and Methotrexate 30 mg/m^2 for four cycles, Mitomycin/C 7 mg/m^2 for two cycles). All patients completed chemotherapy except one who withdrew after the first cycle for psychiatric reasons. This patient was treated with megestrol acetate 160 mg twice daily. Following completion of 4 cycles of chemotherapy, patients were assessed for therapeutic response.

All but two cases proceeded to mastectomy and axillary clearance. These two patients were considered inoperable because of tumour fixity prior to and subsequent to both chemotherapy and radical radiotherapy.

49 of the remaining 52 patients had post-mastectomy flap radiotherapy receiving 40 Gy in 15 fractions over three weeks (using 10 meV electron beams to the chest wall). Of the three patients who did not receive radiotherapy, one declined, one had a contraindication and one was a breach of protocol.

All patients undergoing mastectomy were given adjuvant hormone therapy with tamoxifen 20 mg daily, while 10 premenopausal women were also given goserelin (as above).

Oestrogen receptor status. In the previously reported trial [5], oestrogen receptor (ER) status was not a significant predictor of response to tamoxifen therapy. In the current trial at randomisation, no account was taken of ER status so this was not routinely performed, but when carried out ER was assessed as an H-score (Abbott) previously described [12]. At diagnosis, only 57 patients had ER determined, but a further 45 cases have recently had ER assayed on the pre-treatment biopsy by the same method.

Statistical analyses

All analyses were carried out using SPPS-X Data Analysis Program (SPSS UK Ltd). Chi-squared contingency tables (with Yate's correction) and Fisher's Exact Test (FE) were used to assess for differences in proportions, as indicated. Comparison of continuous data between multiple groups was by the Kruskall–Wallis test. Disease-free interval and survival curves were compared with Gehan's modification of the Generalised Wilcoxon test with the Lee–Desu statistic. Degrees of freedom were $n - 1$ for all analyses.

RESULTS

Patient characteristics

The median age for the "minimal" therapy group was 62 years (36–73) and 58 years (32–71) for the "maximal" group. Mean maximal diameter of primary tumour for each group was 6.2 cm (2.7–9.0 cm) and 6.5 cm (3.0–10.5 cm), respectively. The median follow-up is 30 months for both groups.

Initial response to therapy

The response for "minimal" therapy patients was complete for 2, partial for 17, disease stasis for 17 and initial progression within the first 6 months occurred in 17 patients. Overall, 68% (36/53) of patients had an objective or static response to initial hormone therapy. For "maximal" therapy patients, 5 had a complete clinical response, 26 a partial response, 21 remained static and 2 patients progressed during chemotherapy. The objective response rate to pre-operative chemotherapy was 57% (31/54).

Comparison of outcome between treatment groups

In follow-up, the proportion of patients developing distant metastases was similar for the two groups (hormone therapy 43%, multimodal 45%), and there was no significant difference in survival (Figure 1).

35 patients failed hormone therapy at a median of 18 months. 32 patients had local progression or loco-regional relapse, while 3 developed metastases as their first site of recurrence. 12 patients developed loco-regional recurrence after multimodal therapy.

A comparison of the total number of treatments required for loco-regional control (Table 1) shows that, in the multimodal group, the mean number of treatments is higher. The types of treatment required for loco-regional control following failure of initial hormone therapy were: radiotherapy for 24 cases, hormone therapy for 18, mastectomy for 9, chemotherapy for 7 and two patients had a simple excision of local recurrence. Following initial multimodal therapy, treatments for loco-regional control were: hormone therapy for 7 cases, chemotherapy for 5, excision of local recurrence for 5 and one patient received radiotherapy (having not received it as part of the initial treatment combination). Uncontrolled local recurrence defined as untreatable chest wall disease with ulceration occurred in 4 patients who received primary hormone therapy and subsequent further treatments and 2 patients who had multimodal therapy.

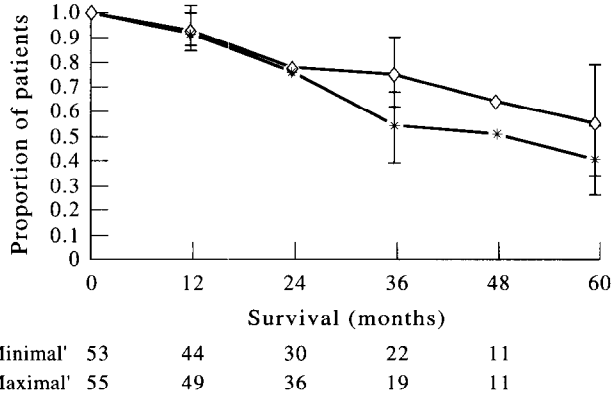

Figure 1. Survival outcome shows no significant difference between patients treated in the "minimal" arm (median >60 months, statistic + 0.97, $P = 0.32$) compared to the "maximal" arm (median = 43 months) (95% CI shown as vertical bars).

Table 1. Number of treatments required for loco-regional control including initial therapy

No. of different treatments	Hormone therapy group (No. of patients)	Multimodal therapy group (No. of patients)
1	21	0
2	15	0
3	10	5
4	5	39
5	0	6
6	2	5
Total	113	231
Mean	2.13	4.20

Oestrogen receptor status

The ER level in primary tumours for the minimal arm was significantly higher in responding patients compared to those with initial progression (Table 2). For purposes of analysis, patients with low or negative ER status (H Score <5) were compared with ER-positive tumours (H Score ≥5). The proportion of ER-positive patients in the "minimal" arm was 71% (35/49) and 53% (28/53) in the "maximal" arm (no significant difference, $P = 0.09$, $\chi^2 = 3.0$).

Response to initial hormonal treatment was more likely for ER-positive than ER-negative tumours ($P = 0.008$, $\chi^2 = 7.02$) (Table 3), but ER status did not predict objective response to chemotherapy (ER-negative 14/25, ER-positive 15/28, $P = 0.95$, $\chi^2 = 0.00$).

ER-negative tumours had a significantly shorter duration of response to hormone therapy than ER-positive tumours (ER-negative median time to loco-regional progression <6 months, ER-positive median = 26 months, $P = 0.005$, statistic = 7.61). Patients with ER-negative tumours (7/25) were no more likely to develop loco-regional recurrence after multimodal therapy than ER-positive tumours (5/28) ($P = 0.58$, $\chi^2 = 0.30$).

A separate comparison of only the patients in the study with ER-negative tumours shows that the 14 who received initial hormone therapy received a total of 33 therapies (mean = 2.36 treatments per patient) for loco-regional control, compared to 109 treatments for the 25 patients

Table 2. "Minimal" arm: level of ER in primary tumour and initial response to hormone therapy

Initial response	No.	H score (Mean (SD))
Complete	2	158 (± 18)
Partial	16	115 (± 73)
Static	15	106 (± 81)
Progression	16	36 (± 38)

Overall comparison $\chi^2 = 12.0$, $P = 0.0007$.

Table 3. Initial response for "minimal" arm and ER status

Response	ER-positive ($n = 35$)	ER-negative ($n = 14$)
Complete	2 (6%)	0 (0%)
Partial	15 (43%)	1 (7%)
Static	11 (31%)	4 (29%)
Progression	7 (20%)	9 (64%)

(mean = 4.36) who received multimodal therapy. In this subgroup, uncontrolled local disease occurred in 3/14 (21%) of the initial hormone therapy group compared to (1/25, 4%) in the multimodal group. This was statistically non-significant ($p = 0.12$, Fisher's Exact Test).

DISCUSSION

The difficulty in determining a standard management approach to locally advanced breast cancer has been related to the fact that the term locally advanced breast cancer covers a wide spectrum of disease, from slowly growing endocrine sensitive tumours to aggressive inflammatory cancers [13]. Many authors have suggested that clinical trials are needed to both further define the disease and refine treatment combinations [1, 13, 14]. Trials investigating the role of hormone therapy in the management of locally advanced breast cancer are limited [3]. In a large EORTC trial [15], the inclusion of either hormone therapy, chemotherapy or both, in addition to local therapy, showed a significant benefit for disease-free survival in all systemic therapy groups in comparison to local treatment alone. The advantage for the hormone treated group was similar to that in patients given chemotherapy. However, two small studies have failed to show an advantage for addition of tamoxifen to chemo-radiation therapy [16, 17]. The potential role of initial hormone therapy in locally advanced breast cancer was studied by Veronesi and associates [18] who treated 46 patients with tamoxifen for 6 weeks and 8 had an objective response. A report of 61 patients receiving pre-operative hormone therapy [19] gave a 39% "regression rate". The latter is similar to the current trial and to our previously published experience [5].

The potential of ER status for predicting initial response to tamoxifen in locally advanced breast cancer has been previously reported [19]. This report confirms that finding (Table 3), but it is apparent that 36% of patients with ER-negative tumours had an initial partial or static response to tamoxifen for at least 6 months. This high proportion may indicate that the initial biopsy sample may not be representative of the overall ER status of the tumour. ER is a heterogeneously expressed antigen increasing the possibility of a sampling error, particularly in a large tumour. It is also possible that the antigen may be lost in the centrally necrotic part typical of large tumours. Despite the high initial progression rate for ER-negative tumours on hormone therapy (Table 3), these patients have still received less treatments on average than those with ER-negative tumours receiving multimodal therapy. There was a non-significant increase (3 versus 1) in the proportion of ER-negative tumours with uncontrolled local disease in the hormone group compared to the multimodal group, which requires careful follow-up.

In this trial, the initial objective response rate to chemotherapy is similar to a previously published study which used a similar MMM chemotherapy regimen, where Gazet and associates [20] had a 53% objective response rate. In a separate study where MMM was administered over 6 months, a 69% objective response was observed [21]. Clearly the response to pre-operative chemotherapy depends on both the type and duration of chemotherapy administered. The regimen used in our trial was well tolerated, while some others have been associated with significant toxicities [15, 22]. While chemotherapy is more rapid in obtaining a response compared to initial hormone therapy, it is unclear whether rapidity of response is important. Indeed, in a study where patients received pre-operative hormone or chemotherapy for three months, there was no difference in early outcome between the groups [20]. Here, there was no significant difference in survival outcome (Figure 1).

In this trial the number of patients with loco-regional relapse after multimodal treatment was much less than those treated with hormone therapy. However, since the multimodal group have virtually all received four therapies for loco-regional control, a more valid comparison is the number of treatments required to maintain loco-regional control for each group. This shows that, while the majority of patients failed hormone therapy, at current follow-up, 40% have received initial hormone therapy as their sole treatment for loco-regional control. Further, overall comparison of the two groups shows that the multimodal group have, on average, received a greater number of treatments than the hormone therapy group. While it is recognised that the greater proportion of ER-positive tumours in the "minimal" group may be a factor in this outcome, the use of fewer treatments does not appear to have compromised the systemic outcome or loco-regional control. After initial multimodal therapy, the treatment options for loco-regional relapse are somewhat limited. In comparison, few patients in the hormone treated group have undergone mastectomy which is a future option likely to remain available to many.

A number of authors have concluded that tamoxifen as the sole therapy in locally advanced breast cancer has a limited role because of low response rates, and is only appropriate for elderly/unfit patients [10, 23]. This trial suggests that initial multimodal therapy offers no significant advantage over sequential use of treatment in locally advanced breast cancer. While further therapy for loco-regional control will be required for the hormone treated group, it is possible that consecutive rather than multiple initial use of therapies in locally advanced breast cancer may allow some patients to avoid unnecessary treatment and associated morbidity. Given the small size of this study, and the possibility of type 2 statistical error, it is important that these findings are investigated in larger trials.

The initial use of hormone therapy was adopted in this trial because it was the minimal single therapy. While it is recognised that some patients may not receive potentially curative surgery with this approach, the long-term survival outcome of patients with locally advanced breast cancer suggests that this is a minority. Given our previous finding of similar local and systemic outcome for radiotherapy and tamoxifen [5], radiotherapy could be used as initial treatment. Alternatively, given the high rate of loco-regional relapse, mastectomy and adjuvant hormone therapy may be a better combination with radiotherapy and chemotherapy in reserve for recurrence. In general, the aim should be to

individualise patient management based on patient and tumour biological factors.

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