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Primary Medical Therapy for Operable Breast Cancer

JANINE L. MANSI, IAN E. SMITH, GERALDINE WALSH, ROGER P. A'HERN, CLIVE L. HARMER, H. DUDLEY SINNETT, PETER A. TROTT, CYRIL FISHER and J. ALAN McKINNA

The Breast Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, U.K.

Abstract—*Fifty-seven patients with large but potentially operable primary breast cancer were treated with primary medical therapy rather than initial mastectomy, using chemotherapy* (15) *or endocrine therapy* (42) *with the tumour remaining* in situ. *Of patients treated with chemotherapy, one* (7%) *achieved a complete remission, and eight* (53%) *a partial response (overall response rate* 60%). *Only one patient had progressive disease while on chemotherapy. Of patients who received endocrine therapy, one* (2%) *achieved a complete response, and* 19 (45%) *a partial response (overall response rate* 47%). *Two patients progressed on endocrine therapy. Only* 10 *patients have so far had a subsequent mastectomy* (18%), *and* 17 (30%) *have had radiotherapy and/or conservative surgery. The rest are still on medical therapy.*

With a median follow-up of 19 *months (range* 6–42 *months) only two patients have had a local recurrence after being disease-free and none have developed uncontrollable local recurrence. Eight* (14%) *have developed distant metastases and four* (7%) *have died of metastatic disease.*

Primary medical therapy may offer an effective alternative to mastectomy for patients with operable breast carcinomas too large for conservative surgery and merits further study.

INTRODUCTION

IN RECENT YEARS there has been a trend away from mastectomy and towards conservative surgery for early breast cancer, justified by similar survival results for each approach [1, 2]. However, for patients with larger tumours conservative surgery is often not feasible and mastectomy remains widely used as treatment of choice. The prognosis for the majority of patients with large tumours is usually poor, even when technically operable with mastectomy [3, 4] and the main rationale for this approach is therefore local control; for many women this is an unattractive option unless no other choice is available.

We have been assessing the role of primary medical therapy (chemotherapy or endocrine therapy) in the initial management of patients with potentially operable early breast cancer who would otherwise require mastectomy. The main aims of the study have been to assess response to medical therapy taking advantage of the *in situ* primary as a measure of treatment sensitivity, and to see whether mastectomy could be avoided. In addition, we have examined the roles of serial mammography, cytology and histology in helping to predict clinical response. This is a new approach to treatment, although in contrast to ourselves other groups have reported similar studies as a prelude to mastectomy [5–10].

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Address for correspondence and reprints: Dr. I.E. Smith, The Breast Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, U.K.

PATIENTS AND METHODS

Patients

From 1985 to 1988, 57 patients with potentially operable, usually large, primary breast cancer attending the Royal Marsden Hospital in Fulham Road, London were included in the study. Most would have required a mastectomy by virtue of size, central site or large tumour:breast ratio. The option of surgery or primary medical therapy was offered to each patient prior to entry to the study. Patients with T1 or T2 tumours who refused even conservative surgery were also included, together with a patient who had a large axillary mass consistent with a breast primary but no breast lump. Patients with inflammatory breast cancer were excluded. Details of T stage, clinical axillary node status and menstrual status are given in Table 1. The median age of the patients was 52 years (range 24–84).

Table 1. Patient characteristics

	Chemotherapy	Endocrine therapy
T stage		
T0	0	1
T1	0	3
T2	4	19
T3	6	11
T4	5	8
Nodal status		
N0	2	9
N1	11	28
N2	2	5
Menopausal status		
Prc	14	9
Post	1	33
Mean age	41 (24–53)	62 (29–84)

Figures in parentheses = range.

Pretreatment evaluation and follow-up

The diagnosis of carcinoma was confirmed by Trucut biopsy (25 patients) and/or fine needle aspirate cytology (48 patients). Further staging included clinical examination with accurate tumour measurement, mammography, full blood count, biochemistry with liver function tests, and chest X-ray. Liver ultrasound and isotopic bone scan were only done if clinically indicated or in the presence of abnormal biochemistry.

Patients were reviewed at monthly intervals whilst on medical treatment for clinical response measurement and assessment of toxicity. Mammograms were repeated after 3 months and then at 6 monthly intervals or sooner if clinically indicated. Response was defined according to the criteria of the International Union Against Cancer (UICC) [11]. A category termed minor response (MR) was also included for patients who had responded clinically but did not reach the criteria to be categorized as a partial response, and stable disease applied to patients who had no change in the size of their tumour for at least 4 months.

In the early part of the study repeat cytology and Trucut biopsy samples were taken in eight patients for direct comparison with pre-treatment samples to determine if changes had occurred as a result of treatment. Failure to see such changes led to these invasive procedures being discontinued.

Treatment

On the basis of data from an overview analysis of adjuvant therapy trials, patients 50 years of age or older received endocrine therapy and those patients under 50 received chemotherapy. However, one patient aged 53 received chemotherapy and nine patients under 50 received endocrine therapy after discussion with each patient of possible therapeutic options. Endocrine therapy consisted of tamoxifen 20 mg daily (38 patients) or the LHRH analogue, leuprorelin 7.6 mg depot injection (four patients) monthly. Of the 15 patients treated with chemotherapy, 11 received CMF (cyclophosphamide 100 mg orally daily for 14 days, methotrexate 50 mg i.v. days 1 and 8, and 5-fluorouracil 1 g i.v. days 1 and 8) and four received MMM (methotrexate 50 mg i.v., mitoxantrone 8 mg/m^2 i.v. 3 weekly, together with mitomycin C 8 mg/m^2, 6 weekly).

Eleven patients eventually progressing on first-line endocrine therapy have subsequently been given either second-line endocrine therapy [6] or chemotherapy [5], rather than local therapy as their next treatment.

RESULTS

The median follow-up is so far 19 months, with a range of 6–42 months.

Response to chemotherapy

Of the 15 patients who received primary chemotherapy, one (7%) achieved a complete remission (CR), and eight (53%) a partial response (PR), giving an overall objective response rate of 60%. In addition, two (13%) patients had a minor response (MR), and three (20%) stable disease (SD). Only one patient progressed on chemotherapy and she subsequently received radiotherapy. The median number of courses given was six (range 2–7), and the median number of courses given to achieve maximum response was three (range 1–5). The number of courses given to achieve complete remission was five.

Of the five patients who received chemotherapy after hormone therapy, three achieved a PR, one a MR and one showed SD.

Response to endocrine therapy

Of the 42 patients receiving primary endocrine therapy, one (2%) achieved a CR, and 19 (45%) achieved a PR, giving an overall response rate of 47%. In addition, four (10%) patients had an MR, and 16 (38%) SD for at least 4 months. Two (5%) progressed during the first 2 months on treatment, one of whom subsequently had radiotherapy and one a mastectomy.

The median duration of therapy was 9 months (range 1–38 months). The median time taken to achieve maximum response was 4 months (range 1–15 months).

Cytological and histological evaluation of response

Repeat histological and cytological analyses were undertaken in eight patients to determine if there were any microscopic features such as degeneration,

necrosis or absence of tumour cells that might indicate a response to therapy had occurred. However, the pre- and post-treatment findings were identical for those patients who achieved a PR (3) and for those who had SD (5) independent of the type of therapy given.

Mammographic evaluation of response

A mammographic response to treatment was seen in 14 patients by virtue of a 50% decrease in size. This correlated with the clinical findings in 12 (86%) cases. In 25 patients who had a clinical response it was not possible to quantify the mammographic changes accurately but shrinkage and other features including decrease in spiculation, change in shape, alterations in size, number and shape of calcification, and decrease in thickening and retraction of the involved skin or subcutaneous tissues were seen.

Local control

So far, none of the patients given primary medical therapy has had uncontrollable local disease in terms of fungation, ulceration or local pain. Only two patients, initially disease-free following definitive local treatment, have relapsed locally, at 2 and 7 months after completing treatment. The former had radiotherapy and the latter a mastectomy.

Twenty-seven patients (47%) have so far been referred for local therapy after primary medical therapy: these have included 10 for mastectomy (18%), six for conservative surgery (11%) and 11 for radiotherapy alone (19%). Three patients treated with mastectomy and three with conservative surgery also had radiotherapy.

Eleven patients eventually developed progressive local disease after having stable disease for a median of 9 months (4–16 months). These patients are currently on second-line medical therapy (six endocrine therapy and five chemotherapy).

Distant metastases and survival

Eight of the 57 patients (14%) have relapsed in distant sites, including lung (2), liver (3), and bone (3), at a median time of 10 months after presentation (range 5–27 months).

Four patients have died, all of whom had disseminated breast cancer. This occurred at a median time of 13 months after presentation (8, 13, 13, 27 months). With short follow-up, overall survival by life-table analysis is shown in Fig. 1, giving a projected 3-year survival of 87% (95% confidence interval: 73–100).

Current status

Nineteen patients (33%) are disease-free at a median follow-up time of 10 months (2–32 months) after definitive treatment. Nineteen patients (33%) have stable disease on first-line endocrine therapy at a median follow-up of 18 months (4–25 months) from the initial diagnosis. The rest are currently on second-line medical treatment.

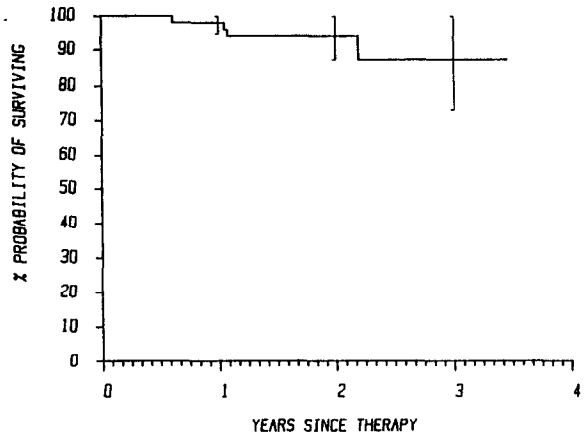

Fig. 1. Survival curve by life-table analysis for the 57 patients in the study.

DISCUSSION

Primary medical treatment as initial therapy for locally advanced *inoperable* breast cancer is well established [12–15], but its use in operable breast cancer is a newer concept.

Our study shows that this approach is feasible, with response rates for chemotherapy (60%) and endocrine therapy (47%), as good as those achieved for metastatic disease. Other studies likewise report significant activity for chemotherapy against primary breast cancer: overall response rates ranging from 70 to 93% and complete remission rates ranging from 9 to 49% suggest that the primary tumour is at least as responsive as metastatic disease and perhaps more so [5–10].

Endocrine therapy alone has recently been evaluated as initial therapy in patients greater than 70 years of age with reported response rates of 61–73% [16, 17]; two randomized studies of tamoxifen versus surgery have shown no difference in overall survival between the two groups [18, 19]. However, only two studies apart from ours have evaluated the use of endocrine therapy in patients with large tumours less than 70 years of age, and similar response rates of approximately 45% were found [6, 20].

Response measurement in our study proved more difficult than we had anticipated. We found considerable interobserver error in measuring the size of the tumour by clinical means and clinical response was not always reflected in clear cut mammographic tumour regression. This was contrary to the findings of Forrest *et al.* [6] where a 100% correlation between mammographic and clinical measurements was reported. We suspect that new criteria for mammographic response to primary medical therapy need to be defined and this problem

will be addressed in detail in a separate paper. No specific changes were seen when pre- and post-treatment cytological and histological specimens were compared, and therefore no information could be gained regarding response to treatment using this investigation. In contrast, other studies have reported features such as tumour necrosis, smudging of cells, lymphocyte infiltration, giant cell formation, stromal oedema and fibrosis in response to chemotherapy [14, 21, 22]. However, these analyses were done on mastectomy specimens and it is possible that Trucut biopsy material is insufficient for detailed histological evaluation.

The optimum follow-up management of residual breast cancer after primary medical treatment has not yet been defined. Most other studies have involved mastectomy after either a fixed number of cycles of chemotherapy [5–7, 10] or at maximum response to medical treatment [8, 9] but our early results suggest that for many patients this may not be necessary. The incidence of local recurrence is so far very low and in particular no one has developed uncontrollable local recurrence. Furthermore, overall survival at present compares favourably with other studies [8, 9] and in this respect randomized trials comparing radiotherapy with mastectomy after primary chemotherapy showed no significant survival difference [10, 23]. Once the optimum choice and scheduling of primary medical treatment and subsequent radiotherapy has been established, then randomized trials will be necessary to determine whether this approach is superior to mastectomy in terms of survival.

Finally, primary medical therapy offers not just the possibility of using the primary tumour *in situ* as an indicator of treatment sensitivity, but also the unique opportunity, through serial needle biopsies, to study biological changes during therapy which might correlate with response and provide some insight into biological mechanisms underlying response.

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