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****** IMPORTANT NOTICE ******

EUROPEAN JOURNAL OF CANCER 1993, VOLUME 29A NUMBER 4, PAGES 592 - 595

Primary Medical (Neo-adjuvant) Chemotherapy for Operable Breast Cancer by Ian A Smith, Alison L Jones, Mary E R O'Brien, J A McKinna, Nigel Sacks and Michael Baum.

THIS ARTICLE CONTAINS ERRORS AND HAS BEEN WITHDRAWN. A CORRECTED VERSION WILL BE PUBLISHED IN A LATER ISSUE OF VOLUME 29 OF THE *EUROPEAN JOURNAL OF CANCER*.

84 patients with large operable breast cancer have been treated with primary medical chemotherapy rather than mastectomy in three sequential studies. 86% had tumours greater than 4 cm in diameter; median diameter was 6 cm (range 1–12). Median age was 46 years (range 23–66). In the first two studies 64 patients were treated with either CMF [cyclophosphamide 100 mg orally days 1–14, methotrexate 50 mg intravenously (i.v.) days 1 and 8, and 5-fluorouracil 1 g i.v. days 1 and 8, repeating at 28-day intervals for six courses] or MMM (mitozantrone 8 mg/m² i.v. three times a week, methotrexate 50 mg i.v. three times a week, mitomycin C 8 mg/m² six times a week, for 8 courses). 69% achieved an overall response including 17% complete remissions. 27% have had local relapse but only 3% uncontrolled local relapse. Only 14% have required mastectomy. In the third study which is ongoing, 19 patients have been treated with infusional FEC (5-fluorouracil 200 mg/m² i.v. 24 hourly by continuous infusion via a Hickman line for 6 months, epirubicin 50 mg/m² i.v. bolus three times a week for 6 months, cisplatin 60 mg/m² i.v. three times a week for 6 months with appropriate intravenous hydration). Overall response rate so far is 84% with 58% complete remissions. There have been no local relapses and no patient has required mastectomy. This study demonstrates that primary medical chemotherapy can be used to avoid mastectomy in the great majority of patients presenting with large operable primary breast cancer. Infusional FEC may be more active than conventional chemotherapy in terms of overall response and complete remission rate, and infusional FEC chemotherapy now needs to be compared with conventional chemotherapy. The concept of primary medical therapy should also be compared with conventional mastectomy followed by adjuvant chemotherapy.
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INTRODUCTION

THE CONVENTIONAL approach to the systemic management of early breast cancer is to give adjuvant chemotherapy or endocrine therapy postoperatively, after surgical excision of the primary tumour. In primary medical therapy (also called neo-adjuvant therapy) the roles are reversed, and chemotherapy and/or endocrine therapy is given as first-line treatment to try to achieve tumour regression before surgery. The origins of primary medical therapy lie in experience gained in the management of locally advanced inoperable breast cancer; here medical treatment has been used increasingly in recent years prior to local radiotherapy to try to improve local control and prolong survival [1].

Our own interest in primary medical therapy at the Royal Marsden Hospital developed from concern about the best management of patients with large but potentially operable breast cancers for whom mastectomy rather than conservative surgery was the conventional option because of tumour size or central position. Such patients have a poor prognosis [2] and the main rationale for mastectomy is, therefore, local control. For many women this is an unattractive option, particularly if the outlook is poor anyway. We have, therefore, been investigating the potential for primary medical chemotherapy, followed if necessary by radical radiotherapy, to achieve local control without the need for mastectomy. Other groups (see Discussion) are now pioneering randomised trials to investigate the influence of this approach on survival.

PATIENTS AND METHODS

Patients

84 patients referred to the Royal Marsden Hospital Breast Unit with histologically or cytologically proven potentially operable breast cancer which would otherwise require mastectomy have been entered into three sequential studies from 1986–1992. 72 of these (86%) had tumours with the maximum diameter of greater than 4 cm, and the median largest diameter of the tumour has been 6 cm (range 1–12). Their median age was 46 years (range 22–66). All were newly diagnosed, and none had received any prior therapy.

Study 1

15 patients were entered into this study between 1985 and 1988 and the main end point was feasibility. Following completion of chemotherapy the decision on whether or not to proceed to mastectomy was left to the referring surgeon. Treatment consisted of either CMF [cyclophosphamide 100 mg orally days 1–14, methotrexate 50 mg intravenously (i.v.) days 1 and 8, and 5-fluorouracil 1 g i.v. days 1 and 8, repeating at 28 day intervals for six courses] or MMM (mitozantrone 8 mg/m^2 i.v. three times a week, methotrexate 50 mg i.v. three times a week, mitomycin C 8 mg/m^2 i.v. six times a week, for eight courses).

Study 2

In this study 49 patients were entered between 1988 and 1991. Here the specific aim of the study was to avoid mastectomy wherever possible. Treatment was with CMF or MMM as described above.

Study 3

In this study which began in 1991 and is ongoing, 19 patients have so far been entered into a new infusional FEC schedule [5-fluorouracil (5-FU) 200 mg/m^2 i.v. 24 hourly by continuous infusion via a Hickman line for 6 months, epirubicin 50 mg/m^2 i.v. bolus three times a week for 6 months, cisplatin 60 mg/m^2 i.v. three times a week for 6 months with appropriate intravenous hydration]. This schedule was developed for primary medical chemotherapy on the basis of promising results in metastatic disease. The aim of this study was to try to improve response and complete remission rates.

Follow-up radiotherapy and surgery

In studies 1 and 2 radical therapy was given electively following chemotherapy to breast and axilla in two phases. Phase I consisted of two tangential portals complemented by a large anterior field and supplemented by a small posterior portal to a dose of 46 Gy given in daily 2G fractions. Phase II was comprised of two tangential portals to encompass the breast plus axilla to a total of 60 Gy over 6 weeks.

Finally, surgery was carried out following radiotherapy at the surgeon's discretion in study 1, and with the aim of avoiding mastectomy if at all possible in study 2.

In study 3, patients are treated with surgery before radiotherapy, providing mastectomy can be avoided.

Endocrine therapy

At the completion of chemotherapy all patients are started on maintenance tamoxifen 20 mg orally daily for a planned 5 years.

Pretreatment evaluation and follow-up

Diagnosis of carcinoma was established by Trucut or Biopty needle biopsy. Further staging included clinical examination with accurate tumour measurement, mammography, full blood count, serum biochemistry and liver function tests, and chest X-ray. More elaborate investigations including liver ultrasound and isotopic bone scan were only carried out if clinically indicated or in the presence of abnormal biochemistry.

Patients were reviewed at monthly intervals while on medical treatment for clinical response measurement and assessment of toxicity. Mammography was repeated after 3 months and then at 6-monthly intervals.

Response was defined according to the criteria of the International Union Against Cancer [3]. A category for a minor response (MR) was also included for patients who had achieved clinical tumour regression but not sufficient for formal definition as partial response.

A subset of patients also had serial colour Doppler breast ultrasound as part of a separate study.

RESULTS

Response to CMF/MMM

In a separate randomised trial for patients with metastatic breast cancer we showed no statistically significant difference in response rates between CMF and MMM [4]. For the purpose of this analysis results with CMF and MMM have been aggregated.

Of 64 patients treated with CMF or MMM 43 (69%) achieved an overall objective response including 11 (17%) a complete remission. A further 9 (15%) achieved a minor response. Only 1 patient (2%) had progressive disease on chemotherapy. The overall reponse rate was further increased to 94% by the addition of radiotherapy as described above.

Of the 19 patients so far entered into infusional FEC, 16 (84%) have so far achieved an overall objective response including 11 (58%) a complete remission. 2 of the remaining 3 patients have had a minor response and 1 so far no change (all only one to three courses so far). No patient has shown progressive disease on treatment.

Local control

For the 64 patients in studies 1 and 2, median follow-up is 2.5 (< 1–6.5) years. 17 (27%) have had a local relapse (including the 1 patient with progressive disease) but only 2 (3%) have had an uncontrolled local relapse.

In study 1 where surgery was left to the discretion of the surgeon 8 (53%) had mastectomy. In study 2, however, where mastectomy was to be avoided where clinically possible only 7 out of 49 patients (14%) had mastectomy and these included 2

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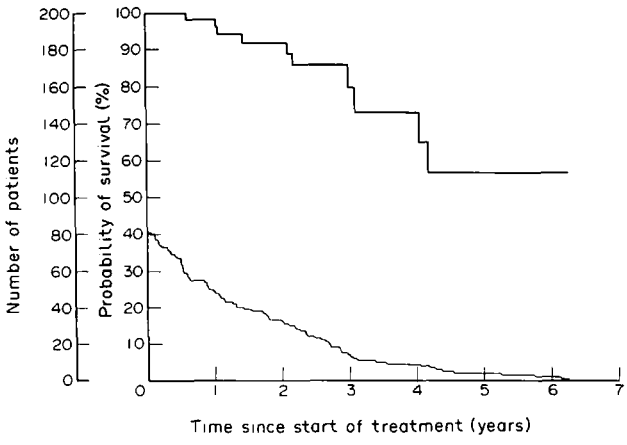

Fig. 1. Survival (life table analysis) of 84 patients entered into primary medical chemotherapy studies Royal Marsden Hospital 1986–1992.

Table 1. Comparative haematological toxicity for CMF/MMM and infusional FEC

	Grade 1–2 (%)*		Grade 3–4 (%)*	
	CMF	FEC	CMF	FEC
Hb	36	65	3	0
WBC	58	59	8	6
Platelets	19	0	8	0

*Worst for any course.
Hb = haemoglobin; WBC = white blood cells.

patients in whom mastectomy could technically have been avoided but who expressed a preference for this.

In study 3 with infusional FEC chemotherapy no patients have so far had local relapse and none have required mastectomy. Follow-up time is short, however, with a maximum of 18 months.

Table 2. Comparative non-haematological toxicity for CMF/MMM and infusional FEC

	Grade 1–2 (%)		Grade 3–4 (%)	
	CMF	FEC	CMF	FEC
Nausea	53	71	10	12
Alopecia	45	53	10	35
Neuropathy	10	59	0	0
Stomatitis	44	59	2	6
Constipation	13	29	0	0
Diarrhoea	25	29	3	12
Lethargy	56	59	5	6
Infection	19	29	2	0
P/P erythema		35		6
Hypokalaemia		6		6
Hickman infection		32		5
Hickman thrombosis		—		11

Survival

Median survival for the whole group of 84 patients has not yet been reached. Predicted 3-year survival by life table analysis is 73% (Fig. 1)

Toxicity

Details of comparative haematological toxicity are given in Table 1 and non-haematological toxicity in Table 2.

DISCUSSION

These results demonstrate that primary medical chemotherapy is a feasible approach for patients with large but potentially operable primary breast cancers and the response rates with conventional CMF or MMM chemotherapy are better than we have obtained in the past for patients with metastatic disease using the same treatment [4]. Subsequent radical radiotherapy increased the response rate to 94% and in study 2 where our main aim was to avoid mastectomy, this was achieved in the great majority (86%) of patients.

Others have reported similar findings. An Edinburgh group reported on 47 patients with operable breast cancer of greater than 4 cm treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy [5]. 34 (72%) achieved significant reduction in tumour volume including 27% with complete clinical regession. This study did not aim to avoid mastectomy. In another study, an Italian group has reported on 157 assessable patients presenting with tumours 3 cm or greater in diameter treated with primary medical chemotherapy using CMF, FAC (5-FU, doxorubicin and cyclosphosphamide) or FEC (5-FU, epirubicin and cyclophosphamide) [6]. 137 patients (81%) achieved tumour shrinkage to less than 3 cm, thus allowing breast conservational surgery rather than mastectomy.

In this type of study local control is an important issue. Local relapse occurred in 27% of patients in studies 1 and 2 on CMF or MMM; it is important to note, however, that some of these patients were salvaged with second-line chemotherapy, endocrine therapy, or radiotherapy and only 14% have required mastectomy. Uncontrolled local recurrence has so far occurred in only 3% of patients. None of the patients treated with infusional FEC have so far had local relapse and this is encouraging, but it should be noted that follow-up time here is extremely short. In the Italian study only 2 patients (less than 1%) are so far reported as having local relapse [6]. In the Edinburgh study the local relapse rate at 3 years is 19% [5]. The time has now come to assess local control achieved by primary medical chemotherapy for large operable breast cancers in a randomised comparative trial against conventional mastectomy with subsequent adjuvant therapy.

It is premature to draw firm conclusions from our current infusional FEC schedule. This treatment was selected for primary medical chemotherapy on the basis of high activity in patients with metastatic disease (71%) and similarly high activity at the Royal Marsden Hospital in patients with advanced gastric cancer, with a response rate around 75% (Dr D. Cunningham, Royal Marsden Hospital). Preliminary results, however, are very encouraging. Although the data are sequential rather than randomised, there is the strong suggestion that this approach achieves a much higher complete remission rate and probably also a higher overall response rate than conventional chemotherapy. The results are now sufficiently encouraging to justify a randomised comparative trial against conventional chemotherapy.

Finally, it is intriguing to speculate whether primary medical

therapy might have a role in the management of much smaller early breast cancers amenable to conservative surgery. Here the justification for such treatment would be improved survival. Studies in experimental tumour systems have shown that non-curative surgery or radiotherapy is associated with stimulation of residual tumour cell growth by a serum growth factor; prior treatment with chemotherapy or tamoxifen suppresses this effect and prolongs survival [7, 8]. A large randomised clinical trial in the U.S.A. and Canada is currently underway to determine whether primary medical chemotherapy will prolong disease-free survival and survival more effectively than the same chemotherapy given postoperatively (NSABP protocol B-18). A similar pilot trial is underway at the Royal Marsden Hospital. Results are not yet available from either of these trials.

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Adjuvant Systemic Therapy in Breast Cancer

H.T. Mouridsen

Systemic adjuvant therapy has improved the prognosis of patients with primary breast cancer. Meta-analyses have demonstrated that approximately one fourth of deaths can be avoided among younger women treated with multiple cytotoxic drug regimens and among older women treated with tamoxifen. However, with the treatments available today many aspects related to the optimal therapy, taking into account the physical, psychological and socioeconomic consequences, are still open. This review discusses some of the major open questions related to the effectiveness of the adjuvant systemic therapy in terms of its ability to reduce recurrence rate and mortality.
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INTRODUCTION

RADICAL LOCOREGIONAL therapy fails to cure approximately 70% of patients presenting with breast cancer [1]. It is now well recognised that subclinical metastases are often established before the clinical detection of breast cancer and therapy directed at the primary tumour fails to affect these metastases.

This is the rationale for adjuvant systemic therapy which was introduced approximately 20 years ago. Until the mid-1980s, however, there was conflicting evidence about the benefit of adjuvant systemic therapy, but the results of the updated meta-analyses of the Early Breast Cancer Triallists Collaborative Group [2, 3] have now ended the dispute about the benefit in terms of reduction of recurrence rate and mortality. In brief, these analyses have demonstrated a highly significant relative reduction in recurrence rates by about 25% and a slightly lower mortality reduction with tamoxifen in patients 50 years old or more and with polychemotherapy or ovarian ablation in patients less than 50 years. Furthermore, direct randomised comparisons have demonstrated polychemotherapy to be superior to single-agent therapy and long-term chemotherapy to be no better than shorter (6 months) regimens.

Thus the introduction of adjuvant systemic therapy has led to an advance in the treatment of breast cancer although it is evident that with the treatments availble today we are far from having achieved a dramatic improvement in the prognosis of breast cancer.

Many questions regarding the optimal therapy, taking into account on the one hand, efficacy and on the other hand, the physical, psychological and socioeconomic consequences, are still open and subject to present and future analysis in clinical trials.

In the following, some of the questions related to efficacy in terms of reduction in recurrence rate and mortality will be addressed.

ENDOCRINE THERAPY

Duration of tamoxifen

Indirect comparisons [2] have indicated that 2 years or even 5 years of adjuvant tamoxifen may be superior to shorter tamoxifen regimens and even outside clinical trials prolonged tamoxifen is now widely used. However, it should be emphasised that the optimal duration needs to be defined from the results of randomised trials and several studies to analyse the importance of duration are now in progress. These trials should also carefully

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