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ORIGINAL ARTICLE

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FILM (5-fluorouracil, ifosfamide, leucovorin and mitomycin C), an alternative chemotherapy regimen suitable for the treatment of advanced breast cancer in the 'out-patient' setting

Abstract FILM, a combination of 5-fluorouracil (5-FU) 750 mg/m^2, ifosfamide 1 g/m^2, leucovorin 200 mg/m^2 and mitomycin C 6 mg/m^2 (alternate cycles), was administered to 24 chemo-naive patients with inoperable disease, locally advanced or metastatic. Up to 6 × 3-weekly cycles of FILM were administered on an out-patient basis. Responses included 8 patients in complete remission (CR) and 12 showing a partial response (PR) (83%). Following analysis of these results, the FILM regimen was introduced as a standard out-patient protocol at the North Middlesex Hospital, United Kingdom. A further 66 patients have been treated in this setting. Retrospective analysis of these data confirm the trial results and allow conclusions regarding tolerability, toxicity, duration of response and survival to be drawn from a total cohort of 90 patients. A total of 524 cycles have been administered. Nineteen cycles (4%) were delayed owing to slow recovery of white blood cells (WBC), but no dose reductions were necessary. Five blood transfusions were required for anaemia. The most frequent non-haematological toxicities included nausea, vomiting and fatigue. Of 80 patients treated for inoperable or locally advanced disease, 56 (70%) remain in remission, and 69 (86%) remain alive after 5 years.

Introduction

Breast cancer is the most common cancer found in women in Europe and the United States. It represents around 20% of all malignancies in women in Europe. The annual incidence of the disease is between 50 and 60 cases per 100,000 with mortality rates of 15–25 per 100,000 [1]. Forty-five percent of all newly diagnosed breast cancers occur in women over 65 years of age.

Survival is determined by a number of factors, most of which are related to the incidence of the development of metastases. The presence of occult micrometastases means that many patients who remain apparently disease-free for long periods of time eventually develop overt metastatic disease regardless of the type and appropriateness of local therapy. Adjuvant chemotherapy has been estimated to give a reduction in the relapse rate of 30% and reduces the death rate by 20% compared with patients not receiving such therapy. The nature, timing, and duration of such adjuvant chemotherapy have not yet been clearly defined despite the intensive work by specialised groups internationally.

Locally advanced disease without overt distance metastatic disease has been shown to respond better to a combined modality approach using chemotherapy given prior to surgery or radiation [2]. Whether this approach results in any increase in overall or disease-free survival remains a subject of debate.

Once metastatic disease has become detected clinically, then the objective of treatment should be to obtain the longest period of disease control with the minimum effect on the quality of that remaining period of life. Active chemotherapeutic agents against breast cancer include alkylating agents (e.g. cyclophosphamide), anthracyclines (e.g. doxorubicin), anti-metabolites [e.g. 5-fluorouracil (5-Fu), methotrexate] and others (taxanes, mitomycin C, vinorelbine), all of which have shown single-agent activity of greater than 27%. When used in combination, the efficacy is greatly increased.

Ifosfamide, used as a single agent in pre-treated patients, has been shown to produce response rates of 12–49%. Experimental evidence has shown a greater activity than cyclophosphamide and also suggests that there is a lack of complete cross-resistance between these two agents [3]. In addition, ifosfamide is not susceptible

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to the multidrug-resistant mechanisms involved in breast cancer and reduces intracellular glutathione levels [4]. It therefore has the potential to improve the response to other agents such as 5-FU, and to prolong the therapeutic benefit by delaying the emergence of resistant cell clones.

This led to the development of FILM – a combination of 5-FU, ifosfamide, leucovorin and mitomycin C, for treatment of advanced breast cancer at the North Middlesex Hospital, United Kingdom. All drugs in this combination have demonstrated antitumour activity in advanced breast cancer [5–10]. The aim was to develop an effective and practical out-patient regimen. The results of this pilot study have been published previously by Davidson et al. in 1998 [11].

Based on the encouraging results seen with the pilot study, FILM was introduced as a standard protocol for use in the routine out-patient clinic at the North Middlesex Hospital. The purpose of this paper is to evaluate and discuss the results obtained with this combination at the North Middlesex Hospital in both settings.

Patients and methods

Inclusion criteria for clinical study

Patients aged 18 years or over with locally advanced, inoperable or metastatic breast cancer were included in the study. To be eligible for the study, the patients needed to have histologically proven breast cancer that had not been treated with chemotherapy previously. The presence of at least one bi-dimensionally measurable lesion was required in order to obtain an objective tumour response. Other eligibility criteria included: performance status [Eastern Cooperative Oncology Group (ECOG)] of 3 or less, life expectancy greater than 3 months, ANC more than 2×10^9/l, platelet count more than 100×10^9/l, serum creatinine below 1.2 μmol/l, serum bilirubin below 35 μmol/l, serum albumen 35–50 g/l, and AST/ALT up to 2.5 times the normal upper limit. Patients were ineligible if they had cerebral metastases, concurrent malignancy or psychiatric disorders. The study was approved by the Ethics Review Committee of the Haringey Health Authority, and all patients enrolled gave written informed consent.

FILM out-patient schedule

FILM was administered as an out-patient schedule. This combination included 5-FU, ifosfamide, leucovorin and mitomycin C, with mesna given as a uro-protectant for the ifosfamide. All components of this regimen were administered on day 1 of each 3-weekly cycle, except for mitomycin C, which was administered at alternate cycles. Up to 6 cycles were administered. The schedule in the out-patient clinic on day 1 of each cycle was as follows.

In general, patients attended the clinic at 10 a.m. Blood samples were taken on arrival. After a clinical assessment and a check on the blood counts, the patients received the anti-emetics ondansetron (8 mg) and dexamethasone (8 mg) as bolus injections in normal saline. Ten minutes later, mitomycin C 6 mg/m^2 (only at alternate cycles), leucovorin 200 mg/m^2 (350 mg max.), 5-FU 750 mg/m^2 (max. 1500 mg), mesna (20% of the ifosfamide dose) were introduced as intravenous boluses into the side-arm of a fast-running normal saline infusion. Ifosfamide 1 g/m^2 was then administered as a 30–40 minute infusion. The total administration time was approximately 90 min. Patients usually left the clinic before 4 p.m. Mesna at 40% of the ifosfamide dose was given orally at 4 and 8 h after the ifosfamide infusion was started. This was prepared in orange juice and given to the patients to take at home. Patients were also given either domperidone capsules (10 mg) to be taken 3 times daily or ondansetron (8 mg) to be taken twice daily as required by the patient. Any radiological assessments required were scheduled on the day prior to chemotherapy.

This regimen was repeated at 3-weekly intervals except for the mitomycin C, which was given on alternate cycles. Treatment could be delayed by 1 week if blood parameters had not recovered. The doses could be reduced by 25% if the platelet nadir was below 10×10^9/l or grade III renal toxicity occurred. Haemopoietic growth factors were allowed if required.

Follow-up treatment

In patients with inoperable local or node-positive disease, the intention was to use FILM as a neoadjuvant treatment. Therefore patients who responded to FILM were offered breast-conserving surgery and/or radiotherapy or were thereafter commenced on tamoxifen as long-term maintenance therapy. Non-responders or patients with progressive metastatic disease were re-evaluated and given other chemotherapy or supportive care as appropriate.

Evaluation of disease and tumour response

Before commencing FILM, each patient had a biopsy of the breast and nodes to determine the disease pathology. The extent of the disease was assessed using mammograms, ultrasound, X-rays and palpation. Other radiological techniques were used as clinically indicated. Bi-dimensional measurements were made using these techniques. In general, physical measurements were taken at each cycle and radiological assessments were conducted at baseline, after 3 cycles and after 6 cycles.

The objective responses were assessed using the standard UICC criteria [11]. Responses were defined as follows: complete remission (CR) was defined as the disappearance of all tumours for at least 4 weeks. Partial response (PR) was defined as a reduction in the size of the measurable tumours by more than 50% for a minimum of 4 weeks. Stable disease (SD) was defined as a reduction in tumour size of less than 50% or an increase of less than 25%. Progressive disease (PD) was defined as an increase of more than 25% in the size of any of the measurable tumours or the appearance of new lesions. If surgery was performed after chemotherapy, the histopathological reports were examined and responses of CR were downgraded to PR if there was any evidence of residual carcinoma. Bone lesions were not regarded as measurable. A subjective assessment was made on the basis of bone scans.

Following completion of treatment, patients were regularly followed up. Time to progression and survival were calculated from the start of treatment. Toxicity was assessed after each course of FILM using the standard World Health Organization (WHO) criteria.

Evaluation of patients treated in routine practice

Following analysis of the results from the clinical study, FILM was introduced to the routine oncology out-patient clinic as an additional treatment protocol for inoperable or advanced breast cancer.

The chemotherapy schedule used was as described for study patients. However, when mesna tablets were introduced, the oral mesna given in orange juice at 4 and 8 h after starting the ifosfamide infusion was replaced with mesna tablets given at 2 and 6 h after the start of the ifosfamide infusion.

Patients were offered FILM only if it was considered the most appropriate treatment. In general, the intention was to use FILM to treat these patients on a neoadjuvant basis, either to render non-operable tumours operable, or shrink the tumour to enable breast-conserving surgery to be used. The staging of the disease and assessment of response was done using standard routine techniques. There was no requirement to have measurable disease. Any

computed tomography (CT) scans, X-rays or other radiological techniques were conducted as clinically indicated.

The data presented here were collected retrospectively from the routine hospital notes recorded during treatment.

Results

To date a total of 90 patients have been treated with FILM.

Twenty-four patients aged 30 to 72 were entered into the study. These included 8 with metastatic disease and 16 with locally advanced or inoperable disease. Three patients had bone metastases only. Although these did not strictly fulfil the inclusion criteria for the presence of measurable disease, they were included and evaluated subjectively. All patients were evaluated for toxicity. The demographics of the patients included are shown in Table 1.

Sixty-six patients (aged 22–69 years) have also been treated with FILM in routine clinical practice. Sixty-four patients were regarded as either inoperable or had locally advanced disease. Two patients had metastatic disease.

Evaluation of tumour response and survival

In the initial study of 24 patients, 6 patients achieved CR and 14 achieved PR after 3 courses of FILM. A further 2 patients in PR achieved CR after 6 courses (Table 2).

Distinct differences in response occurred in metastatic and non-metastatic patients. Of the 16 patients with non-metastatic disease, 8 achieved CR and 8 achieved PR. Five of these patients were shown to have achieved pCR by histopathological confirmation following completion of treatment. In the non-metastatic group, 6 patients had breast-conserving surgery following the chemotherapy. Of the 8 patients with metastatic disease, 4 achieved PR (seven of these patients had bone disease).

Of the 66 patients treated in routine practice, 23 achieved CR and 36 PR (89% response). In 25 of these cases, the data collected allowed objective responses to be obtained according to the UICC criteria.

The data from all patients were combined to analyse the duration of response and survival. At the time this manuscript went to press, neither the median duration of response nor the median survival had been reached for the non-metastatic patients (Figs. 1, 2). Seventy percent of these patients remain in remission and 86% remain alive after 5 years. The Kaplan-Meier analysis suggests that the median time to progression will be over 6 years and the survival period over 10 years. The median duration of response in the metastatic patients was 159 days (approx. 5 months). The median survival of these patients was 645 days (approx. 21 months).

Table 1 Patient characteristics of the study patients (*ECOG* Eastern Cooperative Oncology Group)

No. patients entered	24 (1 male)
Mean age in years (range)	55.2 (30–72)
ECOG performance status	
0	13
1	9
2	2
Menopausal status	
Pre-menopausal	7
Post-menopausal	16
Sites of disease	
Primary	20
Axillary nodes	14
SCF nodes	1
Bone	7
Liver	1
Other soft tissue	1
Tumour stage	
Metastatic	8
T3-T4 Node positive (axillary nodes)	12
T4 Node negative; inoperable	4

Table 2 Response rates of the study patients after 6 courses of FILM (*CR* complete remission, *PR* partial response, *SD* stable disease, *PD* progressive disease)

Objective response	All patients	Metastatic disease	Non-metastatic disease
CR	8 } (83%)	0 } (50%)	8 } (100%)
PR	12 }	4 }	8 }
SD	0	0	0
PD	4	4	0
Total	24	8	16

Tolerability and toxicity

Treatment was well tolerated. Eighty-seven patients (97%) completed the full 6 courses of FILM. Three patients were withdrawn owing to continued progression of the disease. A total of 524 courses were administered. Nineteen courses (4%) were delayed by 1 week due to

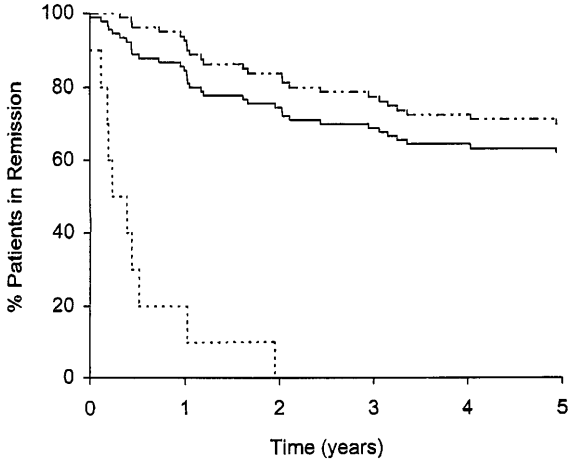

Fig. 1 Time to disease progression following chemotherapy with FILM in patients (a) with metastatic disease (- - - - - - -), $n = 10$; (b) with non-metastatic disease (- - — - - —), $n = 80$; (c) all patients (———), $n = 90$

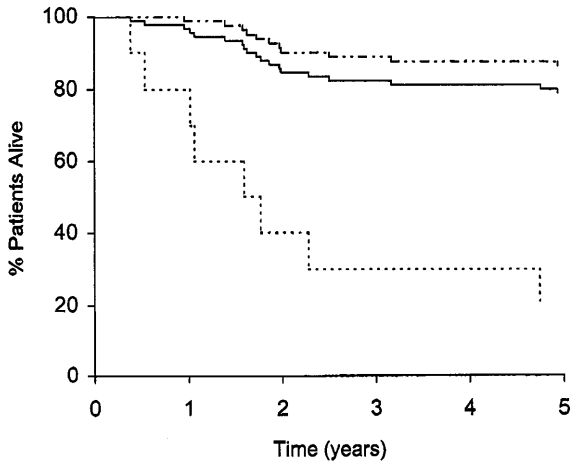

Fig. 2 Survival time following chemotherapy with FILM in patients (a) with metastatic disease (- - - - - - -), $n = 10$; (b) with non-metastatic disease (- - — - - —), $n = 80$; (c) all patients (———), $n = 90$

slow recovery of the white cell count (WBC), but no dose reductions were required. Five blood transfusions were required for anaemia. No patients were withdrawn due to intolerance.

The haematological and biochemical effects of FILM are summarised in Table 3. Leucopenia was the principal toxicity. Leucopenia WHO grade 3 or 4 occurred in 14 (16%) patients. In 1 patient the severity was CTC grade 4, but this occurred in 1 cycle only and recovered fully following a 1-week delay in the next cycle of treatment. No patients experienced neutropenic sepsis. Thrombocytopenia was recorded in 10 patients (11%). Haemoglobin was recorded below normal values in 32 patients (36%), but this was only considered severe enough in 5 patients to necessitate a blood transfusion.

Nausea and vomiting occurred in 53 patients (59%), fatigue in 49 patients (54%), alopecia in 40 patients (44%) and stomatitis in 5 patients (21%). No encephalopathy or haematuria was observed. The severity of the symptomatic toxicity was observed in detail in the study patients. This is shown in Table 4. The majority of side effects were rated WHO CTC grade 1–2. No grade 4 non-haematological toxicities were observed.

Table 3 Haematological and biochemical toxicity in all treated patients ($n = 90$)

	Worst WHO grade observed				
	0	1	2	3	4
Haematological					
Leucopenia	25	27	24	13	1[a]
Thrombocytopenia	80	6	2	2	0
Anaemia	58	24	8	0	0
Biochemical					
Creatinine	90	0	0	0	0
Alkaline phosphatase	84	5	1	0	0
Bilirubin	86	2	1	1	0

[a] Occurred in 1 cycle only

Table 4 Toxic side effects in the study patients ($n = 24$)

	Worst WHO grade observed				
	0	1	2	3	4
Infection					
Stomatitis	19	3	2	0	0
Neutropenic sepsis	24	0	0	0	0
Other	18	5	1	0	0
Gastrointestinal					
Nausea and vomiting	8	7	5	4	0
Diarrhoea	22	1	0	1	0
Constipation	22	0	1	1	0
Other	16	7	1	0	0
CNS					
Encephalopathy	24	0	0	0	0
Dizziness	21	3	0	0	0
Other	21	3	0	0	0
Musculoskeletal					
Fatigue	10	6	7	1	0
Aches/pains of limbs	20	3	1	0	0
Urothelial	24	0	0	0	0
Alopecia	17	2	5	0	0
Cardiac	24	0	0	0	0

Discussion

The results achieved in the initial study were better than had been expected, particularly in the sub-group of patients which had inoperable or locally advanced disease. In this group, all patients completed all 6 courses of chemotherapy. All patients demonstrated at least a partial response, and in 50% of these patients the response was assessed clinically complete. The response rate in the 8 metastatic patients was 50%, reflecting the advanced stage of these patients – 7 of these patients having bone disease.

No patients were withdrawn from the study owing to toxicity, indicating that this regimen is tolerable. The toxicity profile was acceptable, with the major toxicity being leucopenia. In 1 cycle a WHO grade 4 leucopenia was recorded, but this recovered after a 1-week delay and did not occur again after the next cycle of FILM. The main non-haematological toxicities were nausea/vomiting, fatigue and alopecia, but these were considered mild to moderate as the majority of these side effects were rated as WHO grades I or II. Further details of this study have been published previously [11].

These initial study data indicated that the FILM regimen was particularly effective in patients with locally advanced disease. FILM was therefore included as standard treatment protocol for suitable patients attending the oncology out-patient clinic at the North Middlesex Hospital, United Kingdom. In particular, it was offered as a neoadjuvant treatment, either to patients regarded as having inoperable disease with the aim

of rendering the tumour operable, or to those having large primary tumours with the aim of causing shrinkage and thus allowing the possibility of breast-conserving surgery. Since its introduction in this setting, a further 66 patients have been treated. The response rate in this group was 89%, indicating that when taken into routine practice the high response rate is maintained. The toxicity profile of this regimen in routine practice reflected that observed in the study. The most frequent toxicities recorded included leucopenia, nausea, vomiting and fatigue.

It was possible to combine some of the results of the study with data collected from routine treatment to allow conclusions to be drawn on a cohort of 90 patients. The principal dose-limiting toxicity is clearly leucopenia. However, only 4% of the cycles had to be delayed to allow the WBC to recover. No dose reductions were necessary. All other side effects were tolerable to the extent that 87 of the 90 patients treated to date have completed the full course of 6 treatment cycles.

The high response rate achieved in both the study and routine practice is reflected by the duration of response. In the non-metastatic group, only 30% have relapsed and 14% have died after 5 years; therefore, the mean time to progression and survival cannot be determined accurately. The Kaplan-Meier analysis (Fig. 1) suggests that the mean time to progression will be at least 6 years. This is particularly encouraging and compares very favourably with other regularly used first-line regimens such as CMF, FAC or MMM. While the survival rate will depend on various factors including further treatment, the effectiveness of the primary treatment will have a major influence. FILM will therefore have contributed significantly to survival. Kaplan-Meier analysis (Fig. 2) suggests that the mean survival will be at least 10 years.

Used in the neoadjuvant setting, the FILM did not present any practical difficulties in administration. Each component is simply applied to the side-arm of a fast-running intravenous saline infusion. The chemotherapy nursing staff reported no problems with extravasation, which can occur with some forms of i.v. chemotherapy. The total time taken to administer FILM was approximately 90 min. This allows time for blood samples to be taken and results obtained before chemotherapy is administered. In general, patients would attend the out-patient clinic at about 10 a.m. and leave before 4 p.m.

Although ifosfamide has been used extensively for intensive chemotherapy in recurrent disease, there is some reluctance to use it as part of a first-line treatment protocol in breast cancer. This reluctance is related in part to the urotoxicity caused by ifosfamide. However, this can now be avoided with the use of mesna. The i.v. mesna formulation has traditionally been made up in orange juice for oral administration, but this has a very bitter taste, which may contribute to the feeling of nausea. The introduction of mesna tablets allows a more patient-friendly regimen and eliminates this problem altogether.

In summary, the FILM regimen fulfils the requirements of a first-line primary (neoadjuvant) chemotherapy regimen for advanced or inoperable breast cancer. It has the following characteristics:

1. Very effective – the response rate is in the region of 90% and the median time to progression is approximately 6 years.
2. Well tolerated – 97% of patients completed the full 6 courses of chemotherapy. The toxicity profile may be regarded as mild to moderate.
3. Reduces surgery – using FILM in the neoadjuvant setting allows breast-conserving surgery to be considered.
4. Out-patient regimen – the overall clinic time can be as short as 4 h on the day chemotherapy is given.
5. Easy delivery – all components are administered into the side-arm of a fast-running saline infusion over a period of approximately 90 min, with the exception of the oral anti-emetics and mesna, which can be taken at home.

This regimen provides an alternative to the use of anthracycline-based first-line regimes. It has the advantage that it does not cause cardiotoxicity and would allow the use of anthracyclines as a second-line treatment. This simple, cost-effective additional line of attack against breast cancer would delay the need to use the newer more expensive agents such as taxanes. Further research should include a comparison of this regimen with an anthracycline-containing regimen such as FEC or FAC. Comparisons of quality of life and cost-effectiveness should also be considered in addition to the efficacy and toxicity.

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