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The Results of Modified Use of Chemotherapy for Patients with Metastatic Breast Cancer

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We investigated whether modifying standard chemotherapy with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) could improve the outcome of patients with advanced breast carcinoma. We changed the conventional FAC treatment as follows: firstly, we administered oestrogens during the delivery of chemotherapy. Secondly, we administered 5-fluorouracil by continuous infusion. Thirdly, we limited chemotherapy treatment to 12 cycles and did not continue treatment during remissions. We evaluated this modified treatment in 63 patients and compared its results to other treatments results given at this institution. We found that the modified treatment improved the quality of life and survival of premenopausal breast cancer patients.
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INTRODUCTION

WHILE TODAY'S screening techniques detect breast carcinoma at an earlier and more treatable stage, the failure rate of primary treatment remains high. As a result, there continues to be a high proportion of patients that develop metastatic breast carcinoma. Since little progress has been made in developing more effective treatments for advanced disease [1] the rate of mortality from breast carcinoma remains high. Among the hindrances to improving therapy is the emergence of drug-resistant tumour clones, which limit the efficacy not only of newly developed cytotoxic agents but also of drugs used in high-dose chemotherapeutic regimens [2–5]. As a result neither of these promising approaches has prolonged the survival of patients with advanced breast carcinoma.

We have attempted to improve the conventional treatment with 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) as follows: firstly, we administered pulses of oestrogens during chemotherapy infusion in an attempt to increase the growth fraction of oestrogen-responsive tumours. According to *in vitro* experiments [6–8] and *in vivo* findings [9–11], we anticipated that for oestrogen-sensitive breast tumours the tumour mass vulnerable to cell cycle-active cytotoxic drugs would increase 2- to 3-fold. Thus, Lippman observed prolonged time to progression and survival with oestrogen priming [10], while Conte achieved an improved rate of complete remission [11]. Secondly, we delivered 5-fluorouracil by continuous infusion. 5-Fluorouracil is mostly cell cycle-dependent in its cytotoxic activity and its pharmacokinetics are strongly dependent on its mode of administration [12]. As a result, the dose of 5-fluorouracil given by continuous infusion can be increased 3-fold [13]. Thirdly, we limited treatment duration to 12 cycles, taking into account that the average length of efficacy of any chemotherapeutic regimen is 9 months [14–17]. By doing so we hoped to lessen the risk of mutagenic effects that inactive chemotherapy may exert on surviving clones [18–20], and we hoped that, as a consequence, the recurrent tumours would remain more treatable.

This report summarises our experience in applying these modifications to 63 patients with advanced breast carcinoma.

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PATIENTS AND METHODS

Patients

The study opened for patient entry in February 1986, and closed for patient entry in August 1990. Patients with measurable stage IV breast carcinoma who had received no prior chemotherapy treatment and no more than three prior hormonal therapies were eligible for the study, provided the oestrogen receptor status of their tumour was positive or unknown. The performance status of patients, estimated by the Zubrod scale, had to be 3 or less. Patients who had previously received adjuvant chemotherapy were not eligible for the study. They received treatment with either high-dose chemotherapy, if their tumour was oestrogen receptor-negative, or investigational agents studied at the time.

Hormone measures

Plasma 17-β-oestradiol, prolactin and gonadotropin levels were monitored during the first three chemotherapy cycles in the first 36 patients. All blood samples were collected from fasting patients at 8 a.m. Measures were obtained 24 h before the start of chemotherapy (i.e. just before administration of the first oral dose of Premarin), immediately before and 24 and 48 h after initiation of chemotherapy. The tests were performed by the Damon Laboratory, Newbury Park, California. A double antibody assay was used to determine 17-β-oestradiol levels, and an immunoradiometric assay to determine the prolactin levels. The upper normal level for prolactin was 18.5 ng/ml.

Treatment

Treatment was administered over a 5-day period as follows: cyclophosphamide, 500 mg/m^2 intravenous (i.v.) bolus, day 1, doxorubicin 50 mg/m^2 infused over 48 h, days 1 and 2; and 5-fluorouracil 3000 mg/m^2 infused over 72 h, days 3–5. Premarin was given orally (p.o.) at a dose of 2.5 mg 24 h before, and at a dose of 3.75 mg 24 and 72 h after treatment onset. Chemotherapy courses were administered every 3 weeks, provided

granulocytes were above 1500/mm^3 and platelets above 100 000/mm^3, and the non-haematological toxicities had recovered completely. They were repeated for a total of 12 cycles. A premarin dose and time schedule that achieved follicular tissue oestradiol levels during the administration of chemotherapy was chosen.

Toxicity criteria

The tolerance of treatment was monitored by measuring blood counts weekly. Doses of cytotoxic drugs were reduced by 20% if granulocytes dropped below 500/μl and/or if grade 3 or higher non-haematological toxicity developed. Doses of cytotoxic drugs were escalated by 20% if the nadir of granulocytes stayed above 1000/μl during the treatment intervals.

Response criteria

The antitumour efficacy of treatment was determined by measurements of palpable tumours prior to each treatment course, and by imaging of non-palpable tumours after every 3 treatment courses. The product of the longest diameter of the tumor and of its perpendicular was used as the measurement.

The NCI criteria were applied to define treatment responses. Time to tumour progression was calculated from date of entry into the study to date of instituting alternative treatment. Survival from treatment was calculated from date of entry into the study to date of death or date of last follow-up. Survival from metastasis was calculated from date of diagnosis of stage IV breast carcinoma to date of death or last follow-up.

Statistical procedures

The χ^2 test was used to evaluate the significance of associations between prognostic factors and response to treatment and survival, respectively. The SPSS/PC+ Statistics 4.0 software program (Marija J. Norusis/SPSS Inc., Chicago) was used to calculate medians and confidence intervals for response and survival data.

RESULTS

70 patients were registered on the study between February 1986 and May 1990, of whom 63 were evaluable. 4 patients were entered into the study in violation of the protocol, and 3 refused treatment after registration. The characteristics of evaluable patients are summarised in Table 1. Sixty-eight per cent of patients were 50 years or older at the time of entry into the study. 48 patients were postmenopausal, 15 patients were premenopausal. Both oestrogen receptor (ER) and progesterone receptor (PR) were positive in the tumours of 26 patients, either receptor was positive in the tumours of 16 patients, and neither one was known in the remaining patients. Visceral sites dominated the disease manifestation in 38 patients (60%). The liver was involved in 41% of patients. The performance status was 3 in 10 patients. 32 patients had received prior hormonal treatments for stage IV breast carcinoma.

We analysed the study for response at a median follow-up time of 32 months (range 13–50). A total of 616 treatment courses were administered to the 63 patients over the 54-month study period. At the time of analysis all patients had completed chemotherapy, 10 patients remained on study and 22 patients were alive. 34 patients completed the scheduled 12-course treatment.

During the delivery of chemotherapy, Premarin increased plasma 17-β-oestradiol levels into the follicular phase range. Neither age nor treatment duration influenced these Premarin-induced oestradiol levels. As delivery of treatment proceeded, plasma oestradiol levels decreased a little, but remained elevated throughout the cycle. Upon completion of treatment, levels returned in the pretreatment range. As expected, basal plasma oestradiol levels of premenopausal women declined with each consecutive treatment cycle. Basal plasma prolactin levels were slightly lower in premenopausal women than in postmenopausal women. Levels peaked 48 h after treatment onset. At that point the mean level exceeded the upper normal range by 90%. After completion of treatment, prolactin levels gradually returned into the pretreatment range.

A total of 616 chemotherapy courses were administered. The treatment was well tolerated by most patients, as 69% of courses could be administered at the scheduled (zero) dose level, and 23% of courses were decreased by one and 3% by two dose levels because of myelotoxicity. Five per cent of courses were increased by one level. The average treatment interval was 25.6 days. Table 2 illustrates the observed haematological toxicities. The granulocyte nadir at the zero dose level was 900/μl and lasted for a median duration of 9 days. The median platelet count nadir was 174 000/μl. Three treatment cycles were complicated by a fever of unknown origin, and 18 cycles were complicated by a bacteraemia during neutropenia. One patient died during septicaemia and neutropenia. She had received radiation therapy to a painful tumour mass encasing the left brachial plexus simultaneously with chemotherapy. Her tumour had also involved the bone marrow.

Non-haematological toxicity was similar to that of standard FAC chemotherapy. However, mucositis was more common and more severe. Over 50% of courses were complicated by mucositis. In 30% of courses mucositis was grade III. The severity of mucositis progressed with each subsequent treatment course in susceptible patients. One patient required hospitalisation for parenteral rehydration. Patients lost between 5 and 10% of their body weight during treatment. 3 patients developed congestive heart failure, which was the ultimate cause of death in 1 patient. This patient had been off treatment for 6 months at

Table 1. Patients' characteristics

Characteristics	No. of patients	Mean	Median	Range
Age	63	56 years	57 years	38–75 years
Length of DFI	63	52 months	27 months	0–216 months
PS (Zubrod)	63	1.4	1	0–4
No. of metastatic sites	63	2.6	3	1–4
No. of prior treatments	32	2	2	1–3

DFI, Disease-free interval. PS, Performance status.

Table 2. Haematological effects

Dose level*	Patients evaluable/ patients suppressed	No. of courses	Median values: AGC (day) (range) nadir × 1000	Median values: Duration suppressed days	Median values: Platelets (day) (range) nadir × 1000	Median values: Duration suppressed days
−2 (−40%)	3/3	16	1.3 (13.5) (0.8–11.4)	5.5 (1–15)	213 (13) (151–308)	0
−1 (−20%)	25/24	117	0.8 (16) (0.0–4.3)	10 (2–19)	139 (13) (24–568)	7 (2–17)
0 (starting dose)	57/55	384	0.9 (16) (0.0–6.0)	9 (1–95)	174 (14) (10–580)	7 (1–38)
1 (+20%)	6/5	28	1.0 (16) (0.1–7.6)	10.5 (5–16)	139 (15.5) (46–601)	9 (2–12)

* Changes in parentheses. AGC, Absolute granulocyte count.

Table 3. Unmaintained remission (months)

Criterion	No. of patients (%)	Mean	Median	Range
Complete remission	8 (13)	18+	18+	4–35+
Partial remission	40 (63)	7+	6+	0–29+
PR-positive	28 (44)	9+	9+	0–23
PR-negative	35 (56)	11+	4+	0–36
Premenopausal	15 (24)	16+	15+	0–29+
Postmenopausal	48 (76)	8+	6+	0–36

the time of death. Her cardiac function had been impaired from long-standing hypertension before entry into the study.

10 patients remained on study at the time of analysis. Thirteen per cent of all 63 patients achieved a complete remission, 63% a partial remission, and 20% a minor response or disease stabilisation. The median time to tumour progression (TTP) was 17 months, with a confidence interval that ranged from 12 to 22 months. TTP was 26+ months for patients who achieved a complete remission, 15+ months for patients who achieved a partial remission, and 9 months for patients with disease stabilisation.

Table 3 lists the times of unmaintained remissions. The median time off treatment was 18+ months for patients who achieved a complete remission. For patients who achieved a partial remission it was 6 months. In other words, patients who achieved a complete remission spent 50% of their surviving time off treatment, and patients who achieved a partial remission spent 25% of their surviving time off treatment, in continued remission. Upon discontinuation of treatment all responding patients experienced further improvement in their performance. Moreover, tumour images of lung, liver or bone lesions continued to improve beyond the treatment duration in 20% of patients who received more than 10 cycles.

The median overall survival from entry into study was 29+ months for all patients, with a confidence interval that ranged from 20 to 38 months. The median overall survival was 38+ months for patients who achieved a complete remission, and 27+ months for patients who achieved a partial remission (Table 4). For previously untreated patients, the overall survival was 33+ months and for previously treated patients, 19 months. Of previously untreated patients, 52% remained alive at the median follow-up time of 32 months, as opposed to 19% of previously treated patients. The median survival from metastasis was 36+ months for all patients.

As expected, performance status and disease extent influenced TTP and survival of patients. Conversely, the ER status of tumours influenced neither. However, the menopausal status

Table 4. Survival (months)

Survival		No. of patients (%)	Mean	Median	Range
(A)	By response				
	Complete remission	8 (13)	38+	38+	15–56+
	Partial remission	40 (63)	28+	27+	8+–65+
	Minor response	8 (12)	17	13	7–41
	No change	5 (8)	18	18	2–33
	Progressive disease	2 (4)	8	8	5–11
(B)	By no. of courses				
	≥9	46 (73)	30+	28+	8+–65+
	<9	17 (27)	18+	13+	2–58+

22 patients are alive.

of patients had a significant effect upon TTP and survival: premenopausal women remained free from tumour progression for a median duration of 23+ months and survived for a median duration of 37+ months; postmenopausal women remained free from tumour progression for a median duration of 14 months and survived for a median duration of 22+ months ($P < 0.05$). The 90% confidence interval for survival of premenopausal women was 30–44 months.

47 patients received systemic treatments at the time of disease progression: 32 with hormonal agents (tamoxifen 18, aminoglutethimide 4, Megace 8), and 18 with chemotherapy. FAC was used for reinduction in 7 patients, and 5 experienced a second remission. Chemotherapeutic agents used in second line were vinblastine 5, mitomycin-C 2, etoposide 1, taxol 1, and high-dose chemotherapy 1. The median survival from reinduction was 9 months for all responding patients.

DISCUSSION

We have reported the outcome of a modified standard chemotherapy treatment for advanced breast carcinoma. We expected that the modifications would make the treatment more effective and less toxic, and that as a consequence the survival of patients would be longer. We found that the treatment was effective: only 4% of patients progressed on treatment, and remissions were durable. The treatment was also well tolerated. Only 3% of treatment cycles caused morbidity that necessitated hospitalisation of patients. The one death observed may not have been solely related to toxicity of drug treatment. Treatment also improved quality of life. Thus, patients who achieved a complete remission spent, on average, 50% of their remaining lifetime off treatment, in continued remission, while patients who achieved a partial remission spent, on average, 25% of their remaining lifetime off treatment, with minimal or no symptoms from their disease. For premenopausal women the survival was distinctly longer than expected.

We do not know which one of the factors we modified contributed most to the improvement of our treatment. We expected that oestrogen priming would primarily improve the chemotherapy responsiveness of postmenopausal tumours, since these tumours are more likely to be oestrogen-sensitive and are generally slow-growing. Premarin induced and sustained before and during treatment plasma oestradiol levels that corresponded to an early follicular phase. Thus, premenopausal women experienced on average a 50% increase in plasma oestradiol concentration, while postmenopausal women experienced a 350% increase. Considering the much larger physiological oestradiol fluctuations of the premenopausal state, it is unlikely that premarin has mediated a tumour cell-kinetic effect in these women. Conversely, based on results of *in vivo* and *in vitro* experiments, one would have expected the changes of oestradiol levels that occurred in postmenopausal women to confer a tumour biological effect. We could, however, not discern any association between TTP and either percentage change of basal oestradiol level or peak oestradiol levels, regardless of whether or not we confined the comparison to ER- and PR-positive tumours in these women. Thus, it may be possible that even a 7-fold rise may not have been sufficient in postmenopausal women. A possible explanation might be that the target tissue responsiveness decreases with advancing age (similar to that of corticosteroid receptors) and that as a consequence still higher doses of Premarin would have been necessary for effective priming. Alternatively, it is possible that the non-17-β-oestradiol components of Premarin, once converted into androgens, may have offset the effects of 17-β-oestradiol. Hence, a pure 17-β-oestradiol preparation would have been necessary for achieving a tumour biological effect.

Did long-term infusion of 5-fluorouracil improve the treatment? Unquestionably, administering 5-fluorouracil by continuous infusion is a more effective use of this drug. Thus, improved tolerance allows a 200% dose increase. Being a pure antimetabolite, the cytotoxic activity of 5-fluorouracil is strongly cell cycle-dependent. Hence, one would expect that this particular modulation of treatment preferentially affected the fast-growing tumours. Tumours in younger women are generally thought to grow faster than tumours in elderly women, so it is conceivable that the continuous infusion of 5-fluorouracil mediated the observed long TTP in premenopausal women. There is no established prognostic factor that could explain the improved outcome of these patients. Thus, our premenopausal women were characterised by the following mean values: age 44 years, disease-free interval 16 months, performance status 0.9 and number of organ sites involved with tumour 2.3. The ER was not known in 40% of patients, and the PR was not known in 67% of patients.

By limiting duration of treatment to its expected length of efficacy we hoped to reduce the toxicity of chemotherapy treatment, i.e. we hoped to eliminate the potential mutagenic effects prolonged treatment may exert on refractory tumour cells that survive. If this assumption is correct, we could, as a consequence, anticipate the rate of tumour progression to be slower and the ability to treat recurrent tumours to be better, hence the survival of patients to be improved. It is difficult to ascertain whether this modifying factor took effect. However, inspite of not maintaining remissions, the median TTP was similar in length to that reported in the literature [22, 23]. Furthermore, the median survival from entry into study was comparable with that observed with treatments using high-dose chemotherapy, with or without bone marrow rescue [16, 23].

We conclude that higher doses of oestrogens may be necessary to induce a tumour cell kinetic effect. We further conclude that 5-fluorouracil administered by continuous infusion may increase the cell kill of fast-growing tumours. Finally, we conclude that maintaining remissions with chemotherapy in patients with advanced breast carcinoma may not be necessary, since neither TTP nor survival was shorter than expected in our responding patients, yet their quality of life was substantially improved.

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Steroid Hormone Profile in Postmenopausal Women with Ovarian Cancer

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Raised levels of steroid hormones are not expected in postmenopausal women. Therefore, if detected in postmenopausal women with ovarian cancer, they must be assumed to be related to the presence of the tumour and, therefore, may be of use as tumour markers. Serum levels of CA125, progesterone, 17-hydroxyprogesterone, sex hormone binding globulin and oestradiol were measured in 44 postmenopausal women with ovarian cancer, postsurgery and prior to chemotherapy. The relationship between the four hormone levels, CA125, patient age, stage, residual disease after surgery and differentiation were tested using the Spearman and Kendall rank coefficients. A significant inverse association was found between CA125 and progesterone levels, and CA125 and 17-hydroxyprogesterone. A positive association between 17-hydroxyprogesterone and progesterone was also found, and positive correlations between stage and CA125, and residual disease and CA125 were confirmed.

Key words: steroid hormones, CA125, progesterone, oestradiol, ovarian cancer
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INTRODUCTION

THE IDEA that ovarian cancer may be a hormone-sensitive tumour is attractive, and if true would mean the availability of a large number of therapeutic options in the treatment of this disease. Raised levels of steroid hormones are not expected in any postmenopausal woman, although normal postmenopausal ovaries do continue to secrete steroids other than oestrogen [1]. However, if raised levels were detected in postmenopausal women with ovarian cancer one must assume that they are in some way related to the presence of tumour. Ovarian cancer has