Induction Chemotherapy With Versus Without Hormonal Synchronisation in Locally Advanced Breast Cancer

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Acta Oncologica Vol 36, No. 2, pp. 207–212, 1997

Sixty-nine patients with locally advanced breast cancer were given induction chemotherapy with doxorubicin and cyclophosphamide (day 1) followed by methotrexate and 5-Fu (day 8). Thirty-two of these patients were also given tamoxifen (days 2–6) in an attempt to induce a G1 arrest in cancer cells, and oestrogen (days 7–8) to stimulate proliferation and thus induce a synchronized wave of proliferating cells. The induction therapy response rate was 61% in the series as a whole (n = 69), but was found to be significantly better in the group on the tamoxifen/oestrogen synchronization regimen than in the remainder on chemotherapy alone (82% vs. 43%). This difference was particularly marked in the respective receptor-positive subgroups [90% (9/10) vs. 30% (3/10); $p < 0.001$]. The findings suggest that, in combination with chemotherapy, tamoxifen/oestrogen therapy, given in the sequence outlined here, constitutes a promising regimen for the treatment of locally advanced receptor-positive breast cancer patients.

Received 21 February 1996
Accepted 20 November 1996

Patients presenting with locally advanced breast cancer are characterized by a poor prognosis. In a much cited study, Haagensen & Stout 1943 (1) found a local recurrence rate of almost 50% and virtually no cures at five-year follow-up after radical mastectomy in women with locally advanced breast cancer. Pre- or post-operative radiotherapy improves local control (2, 3), but most patients eventually die of disseminated disease. The addition of multidrug chemotherapy to surgery and radiotherapy has been associated with a tendency towards improved local control and disease-free survival, though the efficacy of the combined regimen and the sequence of radiotherapy, chemotherapy and surgery are still debated (4–9).

Lippman et al. (10–13) treated women with stage IV or locally advanced breast cancer with doxorubicin and cyclophosphamide (day 1) and 5-fluorouracil (5-Fu) and methotrexate (day 8) in 21-day cycles. Between chemotherapy administrations the patients were given tamoxifen (days 2–6) and oestrogen (days 7 and 8). This schedule was based on previous findings by the Lippman group and by others (14–16) showing that tamoxifen induces a G1 arrest in human breast cancer cell lines, and that subsequent oestrogen treatment can stimulate proliferation and induce a synchronized wave of DNA synthesis. The simultaneously proliferating cells were presumed to be sensitive to S-phase specific drugs such as 5-Fu and methotrexate. Overall response was reported to be 61% for stage IV patients and 85% for stage III patients.

The impetus for the present study was the remarkably good remission rates in patients with locally advanced cancer obtained by Lippman et al., who reported a complete remission rate of 50% compared with rates of only 10–20% reported by others. In this study of 69 breast cancer patients, about one half of whom underwent tamoxifen/oestrogen synchronization in addition to chemotherapy, we confirmed the remission rates achieved by Lippman and colleagues, but also found evidence to show that patients with receptor-positive tumours in particular benefit from synchronization.

MATERIAL AND METHODS

Patients

From January 1987 to July 1991, 69 women with locally advanced breast cancer (Table 1) were given induction chemotherapy. Locally advanced disease was defined as T3-4, N0-3 and/or M1 supraclavicular node involvement, according to the UICC classification of 1987 (17), or postoperative locoregional recurrence. During the first 21 months, 32 consecutive patients (the ACFuMTP group) received chemotherapy plus tamoxifen/oestrogen treatment, and during the following 34 months 37 consecutive

 ISSN 0284-186X

Table 1

Patient characteristics by treatment group

Variable	ACFuMTP	ACFuM	Total	p*
No. of patients	32	37	69	
No. of patients with hormonal status assessed	22(69)**	30 (81)	52(75)	n.s.
Hormonal status				
pos.	10 (45)	10 (33)	20 (38)	
				n.s.
neg.	12 (55)	20 (67)	32 (62)	
Median age (range)	53 (25–81)	55 (31–73)	54 (25–81)	n.s.
Menopausal status				
Pre	16 (50)	16 (43)	32 (46)	n.s.
Post	16 (50)	21 (57)	37 (54)	
Stage				
III	7 (22)	19 (51)	26 (38)	
IV	17 (53)	12 (32)	29 (42)	0.043
recurrence	8 (25)	6 (16)	14 (20)	

* Fisher's exact test. ** = %. For abbreviations please see text.

patients (the ACFuM group) received the same chemotherapy without tamoxifen/oestrogen treatment. In all cases the breast cancer diagnosis was confirmed by biopsy or fine-needle aspiration. In patients operated before chemotherapy axillary nodal status was assessed by dissection (n = 25), in the remainder by clinical examination (n = 44). Fifty-five patients had primary disease and 14 local recurrences. Breast surgery had been performed in all patients with recurrent disease and in 11 patients with primary disease before chemotherapy (Table 2). All patients were examined for distant metastases with lung x-ray, bone scan, and liver enzyme analysis. Distant metastases were detected in 20 patients at the start of chemotherapy. These, along with supraclavicular node-positive patients, were classified as stage IV patients.

Tumour oestrogen receptor (ER) and/or progesterone receptor (PgR) content was measured with an enzyme immunoassay in 75% of cases (n = 52), either in surgical specimens (n = 24) or in fine needle aspirates (n = 28) (18). The measurement was done in primary tumour material in 49 cases and in local recurrence material in 3 cases. All measurements were performed in untreated tumour material. Twenty (38%) of the patients were hormone receptor positive (i.e. ER $\geq$25 fmol/mg 12 protein and/or PgR $\geq$25 fmol/mg protein) (19–21).

Median age was 54 years (range 25–81 years). A slight majority (54%) of the patients were postmenopausal, and the remainder premenopausal. There was no significant difference between the two treatment groups in receptor status, age or menopausal status (Table 1). However, there were significantly more stage IV patients in the tamoxifen/oestrogen treatment group than in the group receiving chemotherapy only.

None of the patients had previously received chemotherapy. The Karnofsky index was 70 or more in all cases with the exception of one, where it was only 40 because of painful bone metastases.

Treatment

ACFuM chemotherapy was given to all patients (Table 3). In addition, the first 32 patients (the ACFuMTP group) received tamoxifen and oestrogen before methotrexate and 5-Fu. Chemotherapy was given until no further tumour regression was observed. The ACFuM group received a median of 4 chemotherapy cycles, the ACFuMTP group 5 (range 2–7 cycles). After completion of initial chemotherapy, further treatment varied: mastectomy and irradiation, irradiation only, tamoxifen, second-line chemotherapy, or no further treatment.

Evaluation of response and follow-up

Response to chemotherapy was evaluated according to the UICC criteria (22) by clinical examination every three weeks and x-ray of affected sites. Toxicity was evaluated for each individual chemotherapy cycle according to the WHO criteria (23). The worst toxicity grade for haemoglobin, leucocytes or platelets for each cycle was taken as a measure of haematological toxicity.

After chemotherapy the patients were examined every three months. Investigation for distant metastasis was done only when indicated by symptoms. Local recurrence after initial therapy was confirmed by fine-needle aspiration or biopsy.

Statistics

Kaplan-Meier life-table analysis was used to determine time to local failure, time to progression, and survival, and the log rank test for the statistical evaluation. Fisher's exact test was used for all other statistical analyses.

Table 2

Treatment before study

	ACFuM	ACFuMTP
No treatment		
Primary disease	28	16
Recurrence	0	0
Mastectomy + axillary dissection		
Primary disease	0	7
Recurrence	7	7
Breast-conserving surgery + axillary dissection		
Primary disease	3	0
Recurrence	0	1
Radiotherapy		
Primary disease	0	2
Recurrence	4	4
Tamoxifen > 1 month		
Primary disease	0	1
Recurrence	3	1
Oophorectomy		
Primary disease	0	0
Recurrence	0	2

Primary disease: n = 55, recurrence: n = 14.

RESULTS

Response to chemotherapy

None of the patients had progressive disease, and the treatment response rate [i.e. complete response (CR) + partial response (PR)] was 61% (42/69) in the series as a whole, being almost twice as high in the ACFuMTP group as in the ACFuM group [81% (26/32) vs. 43% (16/37); p = 0.001] (Table 4). In 12 patients who achieved clinically complete response the CR was checked by pathological examination of fine-needle aspirates in 9 cases, of mastectomy specimens in 2 cases, and of biopsy in 1 case, CR being verified in 9 cases and residual microscopic cancer found in 3 cases.

The group difference in (CR + PR) response rates was also striking in the respective receptor-positive subgroups (90% vs. 30%; p = 0.02), but no such difference was found between the receptor-negative subgroups (Table 5). Thus, the receptor-positive patients derived significantly greater benefit from the added tamoxifen/oestrogen treatment, the receptor-negative patients manifesting only a tendency toward benefit.

Time to progression and survival

Median duration of follow-up was 49 months (range 19–79). Median time to local recurrence or progression was 24 months for both treatment groups. Median time to distant recurrence or progression was 16 months for the ACFuMTP group, and 21 months for the ACFuM group (p = 0.33). The overall 5-year survival was 25%. Patients with CR during chemotherapy, with or without hormonal treatment, were characterized by a tendency towards longer time to distant relapse and longer survival as compared to partial or non-response patients, though the differences were not statistically significant.

Compared with the receptor-negative subgroup, the receptor-positive subgroup was characterized by a significantly longer time to distant relapse (p = 0.03), longer survival (p = 0.002) and a tendency toward longer time to local recurrence (p = 0.07).

Table 3

Treatment schedules

Drug	ACFuMTP	ACFuM	Day
Doxorubicin	30 mg/m^2 i.v.	30 mg/m^2 i.v.	1
Cyclophosphamide	500 mg/m^2 i.v.	500 mg/m^2 i.v.	1
Tamoxifen	40 mg/m^2 p.o.		2–6
Premarin	0,625 mg/m^2 p.o.		7–8
5-Fluorouracil	500 mg/m^2 i.v	500 mg/m^2 i.v	8
Methotrexate	300 mg/m^2 i.v.	300 mg/m^2 i.v.	8
Folinic acid	15 mg × 6 p.o.	15 mg × 6 p.o	9–10

Cycle length 21 days

Table 4

Response rates for patients with locally advanced breast cancer treated with chemotherapy

	CR	PR	SD	p*
All patients	18 (26)**	24 (35)	27 (39)	
ACFuM group	4 (11)	12 (32)	21 (57)	
				0.001
ACFuMTP group	14 (44)	12 (38)	6 (19)	

* Fisher's exact test. ** = %

Table 5

Remission rates according to receptor status and treatment

Receptor status	Treatment	Remission rates			p*-value
		CR	PR	SD	
Receptor positive					
	ACFuM	2 (10)**	1 (20)	7 (70)	0.022
	ACFuMTP	7 (70)	2 (20)	1 (10)	
Receptor negative					
	ACFuM	2 (10)	7 (35)	11 (55)	0.274
	ACFuMTP	4 (33)	3 (25)	5 (42)	

* Fisher's exact test. ** = %

Toxicity

Details of toxicity due to ACFuM are presented in Table 6. All patients had reversible alopecia. Most patients experienced nausea and vomiting. Mucositis was common, but rarely to the extent of hindering adequate food intake. As expected, it was more frequent after day 8 treatment and usually lasted longer than nausea. Haematological toxicity was common, but moderate. Leukopenia was the main haematological toxicity, but in most instances could be managed on an outpatient basis. Only three patients were hospitalized for severe infections. There was no treatment-related mortality, and no significant difference in toxicity between the treatment groups.

DISCUSSION

The aim of this study was to assess the effect of induction chemotherapy in a group of locally advanced breast cancer patients, and to investigate the possible advantage of adding tamoxifen/oestrogen as described by Lippman and co-workers.

Table 6

Chemotherapy-related toxicity according to treatment

Side-effect	Treatment	Toxicity WHO grade				
		0	1	2	3	4
Mucositis						
	ACFuM	46*	30	19	5	0
	ACFuMTP	34	37	25	3	0
Nausea						
	ACFuM	8	32	46	11	1
	ACFuMTP	3	28	53	16	0
Alopecia						
	ACFuM	0	0	20	80	0
	ACFuMTP	0	0	19	81	0
Haematological toxicity						
	ACFuM	22	24	38	13	3
	ACFuMTP	0	42	29	23	6

* Percent of administered therapy cycles.

In our series as a whole (n = 69) the ACFuM treatment response rate was 61%, a figure in good accord with those of 65–72% obtained by others using doxorubicin containing chemotherapy regimens in stage III-IV breast cancer patients (7, 8).

Adding tamoxifen/oestrogen to chemotherapy was clearly beneficial in terms of response, the overall (CR + PR) being 82% and the CR rate 44%. These figures are similar to those of 85% and 50% respectively, obtained by Lippman and colleagues in patients with locally advanced breast cancer. In our study, the benefit of hormonal treatment was more manifest in the receptor-positive subgroup, and mainly in terms of the CR rate. Receptor-negative patients manifested no significant difference between treatment arms.

Whether the observed benefit of hormonal treatment was due to the proposed mechanism of cell cycle synchronization and stimulation cannot be answered on the basis of the present findings. In theory, it might just as well have been due to the stimulatory effect of oestrogen per se, or to a purely additive effect of tamoxifen in conjunction with chemotherapy. The question of whether the beneficial effect of tamoxifen/oestrogen treatment depends solely on a stimulatory oestrogen effect or on a true synchronization of cell phases due to the combined action of tamoxifen and oestrogen is not readily answered. One way of settling the issue would be to sample material from the treated patients' tumours just before they start taking tamoxifen and before and after they take oestrogen, and then to compare the samples for changes in cell-cycle phase distribution. Such data would be most interesting but are very difficult to obtain.

However, it seems unlikely that the effect of hormonal treatment was due solely to an additive effect of tamoxifen in conjunction with chemotherapy. Patients received tamoxifen for only five days out of 21 in each treatment cycle. They could not be expected to reach therapeutic serum concentrations during most of the interval, although tamoxifen is fairly slowly metabolized. Furthermore, in

responders the response was recorded after only one or two cycles, which is too short a time for the response to have been due to the cytostatic effect of tamoxifen.

Unequivocal evidence of the benefit of hormonal manipulation has not been reported before. Three randomized studies of this issue (9, 24, 25) failed to show a clearcut advantage of hormonal manipulation, and receptor status was only known in a minority of the patients studied. However, these studies were conducted only on stage IV patients, and in general in metastases the content of ER and PgR receptors is lower than in primary tumours (20, 26, 27). If the presence of hormone receptors in tumour cells is indeed a prerequisite for the effect of hormonal treatment, patients with advanced metastatic disease would not be expected to respond well to such treatment.

The treatment was well tolerated. We found no clinically relevant difference in toxicity between treatment groups. The ACFuMTP group was characterized by 42% grade 1 haematological toxicity compared with 24% grade 1 and 22% grade 0 in the ACFuM group. The groups were comparable with regard to more severe grades of haematological toxicity. Lippman et al. (11) reported no difference in toxicity and no difference in the quantity of drug administered in the two treatment arms. In contrast, Conte et al. (25) reported more myelotoxicity and less drug administered in the syncronization group, and Lipton found signs of accelerated tumour growth in terms of increased bone pain and hypercalcaemia after oestrogen administration (24). No signs of accelerated tumour growth were found in our patients.

The present series was small in size and heterogeneous in terms of stage and of treatment both before and especially after the study treatment. There was no randomization of assignment to treatment groups. Despite these shortcomings, it is reasonable to compare the response rates, especially as none of the patients had previously received chemotherapy and only a few had received hormonal treatment. If anything, the response rate would be expected to be lower in the hormonal treatment group since these patients were at a more advanced stage of disease. It is, however, impossible to draw any conclusions as to the subsequent fate of the patients, for example in terms of time to progression or survival. The data for these variables are included in the results solely to give an idea of the outcome in this series of locally advanced breast cancer patients.

Our data indicate that adding hormonal treatment to conventional ACFuM chemotherapy promotes the response rates among receptor-positive patients. Larger, controlled studies, with detailed information about receptor status, would be desirable to confirm our results.

ACKNOWLEDGEMENTS

We are indebted to H. Andersson for the statistical analyses. The study was supported by the G., A. and E. Nilsson Foundation.

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