PRIMARY SYSTEMIC TREATMENT WITH WEEKLY DOXORUBICIN MONOTHERAPY IN WOMEN WITH LOCALLY ADVANCED BREAST CANCER; CLINICAL EXPERIENCE AND PARAMETERS PREDICTING OUTCOME

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Sixty-three patients (median age 64 years) with locally advanced breast cancer (T3, T4 and/or N2) were treated with primary 'neoadjuvant' chemotherapy given as weekly doxorubicin monotherapy (14 mg/m^2 per dose). Seven patients had solitary distant metastasis at the time of diagnosis. Twenty-eight patients (45%) achieved 'partial response' to primary chemotherapy. Twenty-nine patients (46%) had 'stable disease', and 6 patients (9%) had 'progressive disease' during treatment. Following chemotherapy, 52 patients were subjected to surgery and another 4 patients had surgery performed after radiotherapy. Surgery was considered impossible in only three patients. After a median observation time of 23 months, local recurrences were observed in 2 patients, one with progressive disease and one with stable disease during chemotherapy. Univariate analyses revealed that large tumour size, high histological grade and high mitotic frequency were associated with poor primary response to chemotherapy. Recent studies have demonstrated a correlation between p53-mutations and chemotherapy response.

Stage III breast cancer (T3, T4 and/or N2) has a poor prognosis with respect to overall survival and risk of locoregional relapse (1–4). There is no generally recommended treatment regimen for this group of patients, but current opinion is that they need multimodal therapy to achieve optimal local control. In recent years, treatment regimens including primary, "neoadjuvant" chemotherapy have been preferred and are reported to give at least an improved local control, while the effect on overall survival has been more unclear (5–8).

The advantages of neoadjuvant chemotherapy are obvious because it is possible to evaluate the response by simply measuring tumour size, and an ineffective treatment can be modified or terminated. It also provides initial systemic treatment to a group of patients at risk of having undetected distant metastases. However, there is no general consensus regarding which chemotherapy regimen should be used in the neoadjuvant setting.

In Norway, most patients with locally advanced breast cancer are elderly women. Weekly treatment with doxorubicin in low doses as monotherapy was shown to be effective in metastatic breast cancer (8). This regimen has a low toxicity and is well tolerated by senior patients. The aim of this study was to evaluate the effect of weekly doxorubicin monotherapy in locally advanced breast cancer and to evaluate various parameters predicting the clinical response to anthracycline therapy.

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Material and Methods

Patients. From 1991 to 1994 63 patients (median age 64 years, range 32–85) with locally advanced breast cancer were included in this study. Seven patients had concomi-

Table 1

T- and N-categories for patients with locally advanced breast cancer
Stages III and IV (n = 63)

T	N0	(%)	N1	(%)	N2	(%)	Total	(%)
T2					2		2	(3)
T3	12		20		5		37	(59)
T4	7		9		8		24	(38)
Total	19	(30)	29	(46)	15	(24)	63	(100)

tant solitary distant metastasis (UICC Stage IV) (10), while 56 had Stage III disease (M0) (Table 1).

Staging and treatment. All patients were treated in the same hospital. Initially, they went through a staging procedure including x-ray of lungs, lumbar spine, pelvis, bilateral mammography and liver ultrasonography. Staging of the axilla was based upon clinical examination. An open biopsy of the primary tumour was performed to obtain tissue specimens for histological diagnosis and hormone receptor analysis. Some of the tissue specimens were snap-frozen in nitrogen for scientific purposes. The treatment schedule is presented in Figure 1. Doxorubicin (Adriamycin) was given weekly in doses of 14 mg/m^2 for 16 weeks. The horizontal and vertical diameters of the tumour were measured at week 3, 5, 9, 13 and 16 with calipers. Measurements were performed by one investigator for each patient. To avoid confounding factors from biopsy, bleeding and oedema, diameters measured at week 3 were taken as pretreatment values. The clinical response to chemotherapy was classified according to UICC criteria (10). Following chemotherapy, most patients were subjected to local treatment. Tumours considered technically operable were treated with surgery followed by radiotherapy; otherwise radiotherapy was implemented prior to surgery. Surgery consisted of mastectomy with

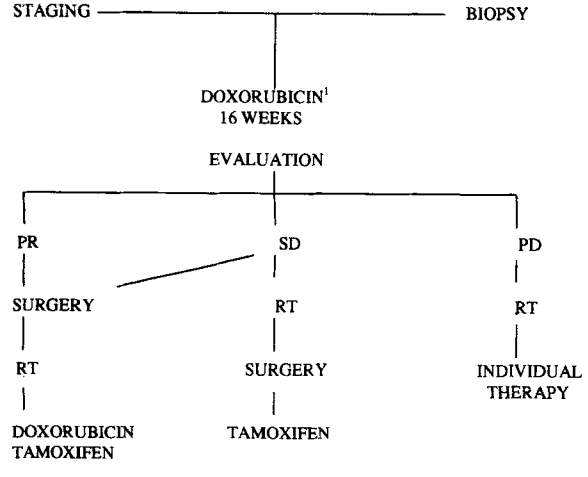

Fig. 1. Treatment schedule. PR: Partial response. SD: Stable disease. PD: Progressive disease (10). RT: Radiotherapy, locoregional.[1] Weekly dose 14 mg/m^2.

exploration of axillary nodes on levels I and II and removal of enlarged nodes suspected to be metastases. Radiotherapy, 50 Gy, was applied to the chest wall and the axilla, and 48 Gy to the supraclavicular area. Patients with complete or partial response to primary chemotherapy, received a second course of 12 weeks doxorubicin after local treatment. All patients with oestrogen and/or progesterone receptor positive tumours received postsurgical treatment with tamoxifen 30 mg a day for 5 years. No patient was lost to follow-up.

Histology. Histological grading was performed using the criteria of Elston & Ellis (11) based on the assessment of tubule formation, nuclear pleomorphism and mitotic counts. In addition, the mitotic frequency (number of mitotic figures pr. 10 HPF, X 400) was recorded separately.

Statistics. Associations between categorical variables was assessed by Pearson's chi-square or by Fisher's exact tests, using the BMDP statistical software. For tumours size and mitotic frequency, individual values were also compared with the Mann-Whitney test. The study protocol was approved by the regional ethical committee.

Results

The primary response to chemotherapy is listed in Table 2. Twenty-eight patients (45%) had partial response (PR). Forty-nine out of 56 patients at Stage III (87%) were subjected to surgery after primary chemotherapy. There was no need for any plastic surgery in form of skin transplantation in this group of patients. Another 4 patients at Stage III were fit for surgery after radiotherapy; one of whom had a skin transplantation (N2). Only three patients (5%), all with progressive disease during primary chemotherapy, were unfit for surgery.

Considering the 7 patients with Stage IV disease, 3 of them had a mastectomy performed after primary chemotherapy, whereas 3 had local control after radiotherapy alone. One patient with liver metastasis had local control from chemotherapy alone. Initial local control was thus achieved in all Stage IV patients.

The chemotherapy regimen was generally well tolerated. Temporary hair loss was the most frequent side effect; most of the patients had to wear a wig for a short period. Three patients developed leukopenia (defined as LPK

Table 2

Primary response to neoadjuvant chemotherapy
Stages III and IV

Response	Stage III	%	Stage IV	%	Total	%
Partial response	24	43	4	57	28	45
Stable disease	27	48	2	29	29	46
Progressive disease	5	9	1	14	6	9
Total	56	100	7	100	63	100

<2.5) during chemotherapy treatment. One of three pts. developed leukopenia during the second (postoperative) course of chemotherapy. She contracted pneumonia and later died. The autopsy revealed diffuse pleural metastases. Post-surgical wound infection was observed in 3 patients, two of whom received radiotherapy prior to surgery.

Owing to a limited number of patients we combined the groups having tumour reduction or growth arrest during treatment (PR + SD) and compared them with the group of patients with progressive disease (PD) during treatment in order to identify parameters predicting response to chemotherapy (12). Univariate analyses revealed that large tumour size, high histological grade and high mitotic frequency all tended to predict a poor response to doxorubicin therapy (Table 3). Tumour size and mitotic frequency were also analysed by the Mann Whitney test, both variables being significant ($p = 0.0005$ and $p = 0.010$, respectively) when comparing the PD group with the other groups. While 21 out of 56 patients with Stage III breast cancer so far have developed distant metastases, locoregional recurrences have been detected in only 2 patients, who both did not respond to primary chemotherapy.

Table 3

Variables evaluated to identify parameters predicting response to chemotherapy Stages III and IV (n = 63). Association between categorial variables assessed by Pearsons chi-square or Fishers exact test. For tumour size and mitotic frequency individual values were also compared by the Mann-Whitney test, see Results

Variables	PR + SD	PD	p-value
Age[1]			n.s.
≤64 years	30	2	
>64 years	27	4	
Tumour category			n.s.
T2	2	0	
T3	35	2	
T4	20	4	
Nodal category			n.s.
N0	16	3	
N1	28	1	
N2	13	2	
Tumour size[2]			0.011
≤67 mm	32	0	
>67 mm	25	6	
Histological grade			0.018
1	18	0	
2	26	2	
3	13	4	
Mitotic frequency[3]			0.011
≤4	32	0	
>4	25	6	

PR: Partial response. SD: Stable disease. PD: Progressive disease (10).
T- and N-categories according UICC (10).
[1] Median age 64 years.
[2] Median tumour diameter 67 mm.
[3] Median mitotic frequency 4 mitotic figures pr. 10 HPF, × 400.

Discussion

Median age of the patients in our study was 64 years, reflecting a high age of many women with locally advanced breast cancer in our country in contrast to other studies reporting a median age of about 50 years (5, 13). It is well known that elderly patients have a reduced tolerance to chemotherapy, and many of our patients would not tolerate the toxic regimens often used in neoadjuvant chemotherapy. Considering the poor outcome of conventional treatment without neoadjuvant therapy in Stage III breast cancer (3, 14) and the encouraging results suggesting neoadjuvant treatment to reduce at least the risk of local relapse, it would be unacceptable to evaluate neoadjuvant chemotherapy against a regimen not including primary chemotherapy. However, we found it, justifiable to evaluate a low-toxic neoadjuvant regimen.

In this study, endocrine therapy was postponed to the postsurgical period. So far, any advantage of early initiation of endocrine therapy combined with primary chemotherapy has not been demonstrated (15). When using chemotherapy and endocrine therapy together it is impossible to know which treatment is the effective one. Thus, combined therapy implies a risk of overtreatment with ineffective chemotherapy in patients responding to endocrine treatment. In addition, this treatment protocol allowed us to evaluate parameters predicting response to a single chemo-therapeutic drug.

Our results show that weekly doxorubicin in the doses administrated was generally well tolerated. Our finding that 2 out of 4 patients treated with preoperative radiotherapy had postsurgical wound infection compared with only 1 out of 52 with surgery prior to radiotherapy corresponds to previous observations (16).

Our clinical response rates are lower, whereas the rate of patients achieving local control is similar, when compared to more toxic neoadjuvant regimens (5–7). A main observation in the study is the low incidence of local relapses. Uncontrolled and early local recurrences are major problems in locally advanced breast cancer. Our results indicate that weekly doxorubicin followed by local treatment in the form of surgery and radiotherapy may reduce the risk of such relapses compared to conventional regimens not including neoadjuvant chemotherapy.

The parameters predicting response evaluated in this study were small tumour size, low histological grade and low mitotic frequency. A few studies have been conducted on locally advanced breast cancer to investigate factors predicting clinical response to treatment. In previous studies neither patient age nor clinical T- and N-categories have been associated with response rates (17). After primary endocrine treatment, Robertson and colleagues demonstrated a significant correlation between high histological grade and high mitotic frequency to lack of response (12). Furthermore one study reports better effect of

chemotherapy in low grade tumours (18). On the other hand, studies have demonstrated high histological grade or high s-phase to be associated with a better response to neoadjuvant chemotherapy (13, 19, 20). The reason for this discrepancy is not clear.

Recent studies are correlating the expression of different parameters associated with chemoresistance (like p-glycoprotein) to the response to doxorubicin therapy. Results so far imply that certain *TP53*-mutation are correlated with resistance to doxorubicin in a subset of patients (21).

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