Dose-dense primary systemic chemotherapy with gemcitabine plus epirubicin sequentially followed by docetaxel for early breast cancer: final results of a phase I/II trial

Andreas Schneeweiss[a], Florian Schuetz[a], Christian Rudlowski[a], Meinhard Hahn[b], Ilka Lauschner[a], Hans-Peter Sinn[c], Dietrich von Fournier[d] and Christof Sohn[a]

We recruited 50 patients with T2–4 N0–2 M0 primary breast cancer into a phase I/II study to define the maximum tolerated dose (MTD), efficacy and tolerability of preoperative gemcitabine (1250 mg/m^2 fixed dose) plus epirubicin (doses escalated from 90 mg/m^2) for 5 cycles followed by 4 cycles of docetaxel (scheduled fixed dose 100 mg/m^2) given on day 1 every 2 weeks (q2w) with pegfilgrastim support. The MTD for epirubicin was 100 mg/m^2, but the docetaxel dose had to be reduced to 80 mg/m^2. Dose-limiting toxicities included fatigue, stomatitis, diarrhea and dyspnea (all grade 3) during gemcitabine plus epirubicin, and fatigue (grade 3) and allergic reaction (grade 4) during docetaxel treatment, respectively. A pathologic complete response could be achieved in 13 patients (pT0 + pTis, 26%), and in the breast and axilla in 12 patients [(pT0 or pTis) + pN0, 24%). Breast-conserving surgery (BCS) was possible in 35 patients (70%). Main grade 3/4 adverse events at MTD were fatigue (57/0%), leukopenia (27/8%), and liver (14/0%) and lung toxicity (14/0%). In conclusion, gemcitabine plus epirubicin 1250/100 mg/m^2 q2w followed sequentially by docetaxel 80 mg/m^2 q2w is highly effective as pre-operative chemotherapy with manageable toxicity. However, response and BCS rates could not be increased by administering gemcitabine plus epirubicin and docetaxel in a dose-dense fashion. *Anti-Cancer Drugs* **16:1023–1028**

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[a]Department of Gynecology and Obstetrics, [b]German Cancer Research Center, [c]Department of Pathology and [d]Department of Gynecological Radiology, University of Heidelberg, Heidelberg, Germany.

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Correspondence to A. Schneeweiss, University of Heidelberg, Department of Gynecology and Obstetrics, Vossstrasse 9, 69115 Heidelberg, Germany.
Tel: +49 6221 567856; fax: +49 6221 567920;
e-mail: andreas_schneeweiss@med.uni-heidelberg.de

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Introduction

In early breast cancer, pre-operative (primary systemic) and post-operative (adjuvant) chemotherapy are equally effective in terms of disease-free and overall survival rates [1]. However, primary systemic chemotherapy (PST) increases the chance of successful breast-conserving surgery (BCS) [2] and, even more intriguing, makes it possible to observe a tumor response to treatment, which is important because the pathologic complete response (pCR) strongly correlates with improved survival [3–6]. Randomized trials have shown that several strategies are useful for increasing pCR rates, e.g. extending PST to more than 4 cycles [6] and sequentially administering single-agent docetaxel following a combination treatment with anthracycline [7,8]. Triple-combination therapies that include gemcitabine with anthracyclines and taxanes also yielded promising pCR rates [9,10]. In particular, the three drugs gemcitabine, epirubicin and docetaxel achieved a pCR rate of 26% [11].

Due to the Gompertzian growth models of breast cancer, it has been hypothesized that administering chemotherapy more frequently, i.e. dose-dense regimens, would be more effective for minimizing and ultimately eradicating the adjuvant tumor cell burden than conventional treatment [12]. In the adjuvant setting this concept has been proven by the Cancer and Leukemia Group B trial 9741, which found dose-dense chemotherapy given every 2 weeks to be more effective in axillary node-positive breast cancer than conventional chemotherapy administered every 3 weeks [13]. Furthermore, pre-operative dose-dense administration of epirubicin every 2 weeks followed by paclitaxel or paclitaxel weekly yielded higher pCR rates than epirubicin and paclitaxel given every 3 weeks [14,15].

Thus, evidence suggests that dose-dense regimens containing gemcitabine, an anthracycline and a taxane may achieve remarkable pCR rates as PST in early breast

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cancer. We conducted this phase I/II study to establish the safety profile, maximum tolerated dose (MTD) and efficacy of gemcitabine plus epirubicin followed by docetaxel given as dose-dense treatment every 2 weeks with pegfilgrastim support.

Patients and methods

Study population

Patients aged 18–65 years were eligible to enter the study if they had histologically confirmed, untreated T2–4 N0–2 M0 monocentric breast cancer with a bidimensionally measurable breast tumor >2.0 (pre-menopausal patients) or >2.4 cm (post-menopausal patients), no distant metastases as assessed by physical examination, abdominal ultrasound, chest X-ray and bone scan, an ECOG performance status ≤ 2 and adequate hematologic (absolute neutrophil count $\geq 1.5 \times 10^9$/l and platelet count $> 100 \times 10^9$/l), hepatic and renal function. Patients were excluded if they were pregnant or lactating, receiving immunosuppressive therapy, had a history of malignancies (except for basal squamous skin cell carcinoma, *in situ* cervical carcinoma or any other tumor that was cured and had not recurred for at least 10 years), active infections, significant neurologic or psychiatric illness, or other disorders that might interfere with therapy or put the patients at additional risk. This study was conducted in accordance with the ethical principles defined in the Declaration of Helsinki and the International Conference on Good Clinical Practice. The study protocol was approved by the Joint Ethical Committee of the University of Heidelberg. All patients provided written informed consent.

Treatment, assessment of toxicity and dose modifications

This single-center phase I/II study was conducted to define the MTD, safety and efficacy of a dose-dense sequential regimen of 5 cycles of gemcitabine (1250 mg/m^2 fixed dose) plus epirubicin (doses escalated from 90 mg/m^2 in increments of 10 mg/m^2) on day 1 every 2 weeks followed by 4 cycles of dose-dense docetaxel (scheduled fixed dose 100 mg/m^2) given on day 1 every 2 weeks with prophylactic pegfilgrastim support (6 mg s.c. fixed dose) on day 2 of each cycle. Patients who developed anemia of any grade received darbepoetin 300 μg s.c. on day 2 of each subsequent cycle. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. MTD was defined as the dose level at which one of three or two of six patients experienced a dose-limiting toxicity (DLT), which was evaluated for each patient during the first 3 cycles of gemcitabine plus epirubicin and the first 2 cycles of docetaxel. DLT included febrile neutropenia (grade 4 neutropenia with a body temperature >38.5°C), grade 4 thrombocytopenia and any grade 3 or 4 non-hematologic toxicity except for grade 3 alopecia, nausea or vomiting. If DLT developed during the 100 mg/m^2 cycle of docetaxel in more than one of three or two of six patients, the doses of docetaxel had to be reduced by 20% to reach MTD. Once the MTD was defined, the patients started treatment at this dose level in phase II of the study. Restarting treatment was delayed until platelet counts had recovered to $>100 \times 10^9$/l and leukocyte counts to $\geq 3.0 \times 10^9$/l. Non-hematologic recovery to lower or equal to grade 1 (except for alopecia) was also required before the start of the next cycle.

Assessment of clinical response

Clinical tumor response was assessed after 3, 5 and 7 cycles, and at the end of treatment. Before the first cycle of chemotherapy and at each re-assessment, the greatest tumor diameter was measured by palpation, breast ultrasound and, if indicated, magnetic resonance imaging. Tumor size was assessed by mammography before the first and after the last cycle of chemotherapy. Clinical tumor response was graded according to RECIST [16], with the size of the tumor at baseline (before administration of the first pulse of chemotherapy) serving as reference.

Surgery, radiotherapy and assessment of pathologic response

Patients proceeded to surgery within 4 weeks after receiving the last dose of chemotherapy. If BCS was not possible, a modified radical mastectomy was recommended. If the tumor size allowed BCS, the following guidelines were observed: (i) surgical margins were free of invasive or non-invasive breast cancer and, if required, repeat excision was performed; (ii) an adequate cosmetic result was anticipated; and (iii) if cosmetically acceptable, the whole previously involved area was excised. In patients with a clinically complete response (cCR) or an unfavorable ratio of tumor to breast size, a biopsy specimen of adequate size was taken from a representative area. All patients undergoing a breast-conserving procedure received standard radiotherapy to the remaining breast. Radiotherapy to the chest wall or regional lymph nodes was performed according to national standards.

Immunohistochemistry

Tumor tissue from the core biopsy was embedded in paraffin and the tissue cut into sections (around 2 μm). Sections were stained using an automated immunohistochemical technique (BioTek TechMate; BioTek Solutions, Newport Beach, California) with strict adherence to the staining protocol. The following primary antibodies were used (clones in brackets): HER2/*neu* (A0485), Ki-67 (MIB-1), p53 (DO7), Bcl-2 (124), estrogen receptor (ER) (1D5) and progesterone receptor (PgR) (PR88) (all reagents from DakoCytomation, Ely, UK). Hormone receptor positivity was assumed when the semiquantitative score was ≥ 3 points (out of a maximum of 12 points). Antibody staining was recorded as the percentage

of positive tumor nuclei for Ki-67 and p53. Bcl-2 and HER2/*neu* immunoreaction was scored from 0 to 3, only with respect to cell membrane staining. In the case of a HER2/*neu* score 2+, fluorescent *in situ* hybridization (FISH) was performed.

Statistical analysis

Descriptive statistics were used to report the relative cumulative dose of chemotherapy (cumulative dose administered divided by scheduled dose), relative dose intensity of chemotherapy (dose administered per week divided by dose scheduled per week), toxicity, and clinical and pathologic response rate. Multiple baseline characteristics of patients treated at MTD were dichotomized and analyzed for their possible effect on achieving a pCR using the χ^2-test. Variables included age (≤ 50 versus > 50 years), histology (ductal invasive versus non-ductal invasive), largest tumor diameter as measured by ultrasound (≤ 5 versus > 5 cm), clinical nodal status (N0 versus N+), grade (1–2 versus 3), ER and PgR status (positive versus negative), HER2/*neu* expression [positive (defined as score 3+ or score 2+ plus FISH-positive) versus negative], Ki-67 (≤ 50 versus $> 50\%$ positive nuclei), p53 (≤ 50 versus $> 50\%$ positive nuclei), Bcl-2 (0–1+ versus 2–3+) and achievement of partial remission after the first 3 cycles (6 weeks) of chemotherapy (yes versus no). Analyses were performed on an intent-to-treat basis, but patients with missing values for these factors were excluded. Statistical tests were performed using SYSTAT software (version 7.0; SYSTAT, Witzenhausen, Germany).

Results

Patient and tumor characteristics

In total, 53 patients were enrolled between July 2003 and May 2004. Of these, three patients were ineligible, two who withdrew consent after the first cycle of chemotherapy and one in whom sarcoma was found in the breast. The remaining 50 patients were included in the efficacy and safety analyses. Baseline characteristics of those patients are summarized in Table 1. Eligible patients received a total of 247 cycles of gemcitabine plus epirubicin (median 5, range 2–5) and 167 cycles of docetaxel (median 4, range 0–4). In total, 182 cycles of gemcitabine plus epirubicin and 122 cycles of docetaxel were administered at the MTD. Toxicity could be assessed for all cycles and response for all eligible patients.

Table 1 Baseline patient characteristics

	n (%)
Eligible patients	50 (100)
Age (years) [median (range)]	46 (29–65)
Tumor size (by ultrasound) (cm) [median (range)]	3.4 (2.1–10.0+)
Histology	
ductal	44 (88)
lobular	4 (8)
tubular	1 (2)
medullar	1 (2)
Histological grade	
1	2 (4)
2	24 (48)
3	24 (48)
Clinical nodal status	
N0	19 (38)
N+	31 (62)
Hormone receptor expression	
ER or PgR positive	34 (68)
ER and PgR negative	16 (32)
HER-2/neu expression	
0 to 1 or 2+ and FISH negative	36 (72)
2+and FISH positive	1 (2)
3+	13 (26)
Ki-67 expression (%)	
≤ 50	33 (66)
>50	16 (32)
unknown	1 (2)
p53 expression (%)	
≤ 50	39 (78)
>50	10 (20)
unknown	1 (2)
Bcl-2 expression	
0–1+	32 (64)
2–3+	17 (34)
unknown	1 (2)

Table 2 Dose escalation and DLTs

	Dose Level 1	Dose Level 2 (MTD)
Gemcitabine (mg/m^2)	1250	1250
Epirubicin (mg/m^2)	90	100
Docetaxel (mg/m^2)	100	80
n	13	6
DLT (during gemcitabine plus epirubicin)	3[a]	2[c]
DLT (during docetaxel)	12[b]	2[d]

[a]Fatigue ($n=2$), stomatitis and diarrhea ($n=1$) (all grade 3).
[b]Fatigue ($n=11$), pain ($n=3$), skin toxicity ($n=2$), infection ($n=1$), liver toxicity ($n=1$), lung toxicity ($n=1$) and diarrhea ($n=1$) (all grade 3).
[c]Fatigue ($n=1$) and lung toxicity ($n=1$) (all grade 3).
[d]Allergic reaction grade 4 ($n=1$), fatigue and neuropathy grade 3 ($n=1$).

Dose escalation and DLT

The dose-escalation scheme and DLTs in detail are shown in Table 2. At Dose Level 1, only three out of 13 patients experienced DLT during treatment with gemcitabine plus epirubicin. However, 12 out of 13 patients developed DLT during docetaxel therapy. Therefore, the epirubicin dose was escalated to the next dose level as scheduled while docetaxel was reduced by 20%. At this Dose Level 2, one of three and two of six patients experienced a DLT. Dose Level 2 was therefore considered the MTD (5 cycles of gemcitabine 1250 mg/m^2 plus epirubicin 100 mg/m^2, sequentially followed by 4 cycles of docetaxel 80 mg/m^2 day 1 every 2 weeks, supported by pegfilgrastim). During the subsequent part of the study, phase II, another 31 patients were treated at the MTD.

Toxicity

Toxicities for all cycles administered at MTD and all patients treated at MTD are summarized in Table 3 and 4, respectively. At MTD, apart from grade 3 alopecia

during the 182 cycles of gemcitabine plus epirubicin, the main grade 3/4 toxicities were leukopenia (7.1/1.6%) and fatigue (13.2/0%), and during the 122 cycles of docetaxel, fatigue (15.6/0%). No deaths and no grade 4 cardiotoxicity were reported, only one grade 3 cardiotoxicity occured. Among the 37 patients who received the MTD the most severe, clinically relevant side-effects were grade 3/4 leukopenia (27.0/8.1%), one grade 4 allergic reaction with respiratory failure (2.7%), grade 3 fatigue (56.8%), and grade 3 liver (13.5%) and grade 3 lung toxicity (13.5%). There was only one episode of febrile neutropenia. Twenty-six (70.3%) and five (13.5%) patients developed anemia grade 1 and 2, respectively. No severe anemia developed. Patients who developed at least grade 1 anemia received treatment with darbepoetin 300 μg s.c. on day 2 of each following cycle.

Table 3 NCI-CTC grade 3/4 toxicities at the MTD by cycle

	No. cycles (%)			
	Gemcitabine plus epirubicin ($n=182$ cycles)		Docetaxel ($n=122$ cycles)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
leukopenia	13 (7.1)	3 (1.6)	3 (2.5)	0 (0.0)
thrombocytopenia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
anemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
febrile neutropenia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Non-hematologic				
diarrhea	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
stomatitis	2 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)
infection	1 (0.5)	0 (0.0)	1 (0.8)	0 (0.0)
fatigue	24 (13.2)	0 (0.0)	19 (15.6)	0 (0.0)
skin	1 (0.5)	0 (0.0)	4 (3.3)	0 (0.0)
liver	5 (2.7)	0 (0.0)	5 (4.1)	0 (0.0)
lung	4 (2.2)	0 (0.0)	1 (0.8)	1 (0.8)
heart	1 (0.5)	0 (0.0)	1 (0.8)	0 (0.0)
neuropathy	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
nail changes	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
pain	2 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)
allergic reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
alopecia	133 (73.1)	0 (0.0)	119 (97.5)	0 (0.0)

Table 4 NCI-CTC grade 3/4 toxicity at the MTD by patient ($n=37$; worst episode per patient was counted)

	No. patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
leukopenia	1 (2.7)	7 (18.9)	10 (27.0)	3 (8.1)
thrombocytopenia	10 (27.0)	0 (0.0)	1 (2.7)	0 (0.0)
anemia	26 (70.3)	5 (13.5)	0 (0.0)	0 (0.0)
febrile neutropenia	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)
Non-hematologic				
diarrhea	16 (43.2)	2 (5.4)	2 (5.4)	0 (0.0)
stomatitis	13 (35.1)	19 (51.4)	3 (8.1)	0 (0.0)
infection	7 (18.9)	13 (35.1)	2 (5.4)	0 (0.0)
fatigue	3 (8.1)	13 (35.1)	21 (56.8)	0 (0.0)
skin	18 (48.6)	6 (16.2)	3 (8.1)	0 (0.0)
liver	21 (56.8)	8 (21.6)	5 (13.5)	0 (0.0)
lung	17 (45.9)	6 (16.2)	5 (13.5)	1 (2.7)
heart	17 (45.9)	8 (21.6)	1 (2.7)	0 (0.0)
neuropathy	20 (54.1)	6 (16.2)	1 (2.7)	0 (0.0)
nail changes	25 (67.6)	4 (10.8)	1 (2.7)	0 (0.0)
pain	15 (40.5)	17 (45.9)	3 (8.1)	0 (0.0)
allergic reaction	11 (29.7)	2 (5.4)	0 (0.0)	1 (2.7)
alopecia	0 (0.0)	0 (0.0)	37 (100)	0 (0)

Received dose and dose intensity

Twenty-six (70%) of all 37 patients who received the MTD as their starting dose completed the planned treatment course of 9 cycles. Treatment was discontinued after 8 cycles in three patients (due to toxicity in two and one refused further chemotherapy), after 7 cycles in three patients and after 6 cycles in three patients (due to toxicity), and after 5 and 2 cycles each in one patient who refused further chemotherapy. The mean/median (range) relative cumulative dose for gemcitabine, epirubicin and docetaxel was 98/100% (40–100), 97/100% (40–100) and 78/100% (0–100), respectively. Dose reductions were required in 15 patients. The mean/median (range) relative dose intensity for gemcitabine, epirubicin and docetaxel was 98/100% (71–100), 96/100% (62–100) and 86/89% (0–100), respectively.

Response

The clinical and pathological efficacy results are shown in Table 5. Three patients [6%; 95% confidence interval (CI) 0–13%] achieved a cCR and 38 patients (76%; 95% CI 64–88%) achieved a cPR, as assessed by mammography, resulting in an overall clinical response rate of 82% (95% CI 71%–93%). Disease did not progress in any patient during pre-operative chemotherapy. For the 37 patients who received the MTD, the results are nearly identical (cCR rate 8% and overall clinical response rate 81%). No cCRs occurred at Dose Level 1. The pathologic response could be evaluated in all 50 patients. No viable tumor cells were detected in the breast tissue removed from 11 patients (pCR breast 22%; 95% CI 11%–33%; three of 13 patients treated at Dose Level 1, eight of 37 patients at MTD). Another two patients had only residual carcinoma *in situ* (pCR_{INV} breast 4%; 95% CI 0–9%; one of 13 patients at Dose Level 1, one of 37 patients at MTD), yielding an overall pCR rate ($pCR + pCR_{INV}$ breast) of 26% (95% CI 14–38%). A pathologic node-negative status was found in 29 patients (58%; 95% CI 44–72%). No invasive residual tumor in breast and axilla ($pCR + pCR_{INV}$ breast and axilla) could be detected in 24% (95% CI 12%–36%) of patients. All patients received surgical treatment and the breast could be conserved in 35 patients (70%); of these, seven required repeat excision to remove all viable tumor tissue.

Predictors of pCR

Considering the 37 patients treated at MTD, the pCR rate was significantly (P value of χ^2-test < 0.0001) higher in patients with ER-negative tumors (67 versus 4% for ER-positive tumors), PgR-negative tumors (44 versus 5% for PgR-positive tumors), ER- and PgR-negative tumors (67 versus 4% for ER- or PgR-positive tumors), and patients with higher expression of HER2/*neu* (43 versus 20%) and Ki–67 (42 versus 17%). Patients who had at

Table 5 Clinical and pathologic response

Treatment response	Dose Level 1 ($n=13$)	Dose Level 2 (MTD) + phase II ($n=37$)	Total ($n=50$)
	(n)	(n)	[n (%)]
Clinical response[a]			
cCR	0	3	3 (6)
cPR	11	27	38 (76)
cCR + cPR	11	30	41 (82)
NC	2	7	9 (18)
Pathologic response			
pT0	3	8	11 (22)
pTis	1	1	2 (4)
pCR + pCR_{INV} breast (pT0 + pTis)	4	9	13 (26)
pN0	10	19	29 (58)
pCR + pCR_{INV} breast and axilla [(pT0 or pTis) + pN0]	4	8	12 (24)
BCS (with/without repeat excision)	10 (4/6)	25 (3/22)	35 (70)

cCR, clinical complete response; cPR, clinical partial response; NC, no change; pCR, pathologic complete response; pCR_{INV}, pCR with only residual carcinoma *in situ*.
[a]By mammography.

least a partial response after 3 cycles of gemcitabine plus epirubicin (6 weeks treatment) were significantly more likely to achieve a pCR than those who did not (36 versus 7%).

Discussion

We demonstrate that dose-dense PST with 5 cycles of gemcitabine plus epirubicin 1250/100 mg/m^2 followed sequentially by 4 cycles of docetaxel 80 mg/m^2 given on day 1 every 2 weeks with pegfilgrastim support is highly effective and can be safely administered in T2–4 N0–2 M0 primary breast cancer patients. The overall clinical response rate was 82% as assessed by mammography and BCS was possible in 70% of patients. Across all dose levels no invasive residual tumor could be detected in the breast, and in breast and axilla in 26 and 24% of patients, respectively.

In contrast to adjuvant (post-operative) therapy, tumor response to treatment can be observed after primary systemic (pre-operative) therapy in early breast cancer, which becomes increasingly important for accelerating progress in the evaluation of new drugs and strategies as pCR strongly correlates with improved survival [1,3–5]. Several strategies have been successful in significantly increasing the pCR rate, one of which is the sequential addition of docetaxel to anthracycline-based combination PST regimens [7,8,17]. In addition, in accordance with mathematical models of tumor regrowth, pre-operative dose-dense administration of epirubicin every 2 weeks followed by paclitaxel and weekly administration of paclitaxel increased the pCR rate as compared to conventional therapy every 3 weeks [12,14,15]. The pCR rate of 26% in the present study compares favorably with the pCR rates of 19–28% reported by the superior treatment arms of randomized trials [7,8,14,15].

In all, 26 of 37 (70%) patients treated at the MTD tolerated the planned 9 cycles of chemotherapy. The mean relative dose intensity for gemcitabine, epirubicin and docetaxel was well above 85%, which results from the favorable toxicity profile of this regimen. Only one episode of febrile neutropenia occurred. Anemia, while relatively common, rarely exceeded grade 2, which is attributed to our policy of offering darbepoietin to any patient as soon as anemia of any grade appeared. Nevertheless, most patients who discontinued treatment prematurely experienced intolerable non-hematological toxicity, mainly sustained grade 3 fatigue, during dose-dense therapy with docetaxel. Therefore, the mean relative cumulative dose for docetaxel of 78% was rather low if compared with 98 and 97% for gemcitabine and epirubicin, respectively. Other moderate to severe hematological and non-hematological side-effects occurred on average less frequently with the dose-dense regimen than with the gemcitabine, anthracycline and taxane triple PST regimens, which also yielded promising pCR rates of 18–26% [9–11]. Therefore, the combined schedules and the dose-dense sequential schedule seemed to be equally suitable alternatives to the three drugs as PST in primary breast cancer.

However, we were not able to increase response and BCS rates by increasing the dose density. It seems unlikely that results will improve simply by exploring new strategies or new drugs in an unselected patient population. Substantial progress might only be possible by tailoring treatment to selected patients according to specific response-predictive markers [18]. Currently, however, there are no clinically useful predictors of response to any cytotoxic drug used in the treatment of breast cancer [19,20]. In fact, in line with findings from other PST trials, the probability of achieving a pCR in our study was associated with negative hormone receptors [7,21], partial remission after 6 weeks of chemotherapy [21], and higher expression of HER2/*neu* and Ki-67. Despite the high pCR rates of, for example, 67% in patients with hormone receptor-negative tumors, the accuracy of single parameters is uniformly low. Recent

technological advances have made it possible for researchers to scan the expression pattern of thousands of genes in individual tumors, thereby identifying molecular signatures with high accuracy to predict distant relapse or response to PST in early breast cancer [22–25]. Work is in progress to discover and validate a gene expression profile that predicts pCR to gemcitabine, epirubicin and docetaxel containing PST [26].

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