Side-effects of Pre-operative Epirubicin-Paclitaxel Therapy in Primary Breast Cancer Associated with Tumor Biology

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Abstract. *Background: The objective of this analysis is to identify relationships between side-effects, tumor biological factors and response to pre-operative epirubicin and paclitaxel therapy in primary breast cancer. Patients and Methods: The study was completed for 38 primary breast cancer patients (M0) who received pre-operative epirubicin and paclitaxel chemotherapy. Anemia was controlled by epoetin alfa and did not cause deviations from the planned chemotherapy schedule. Results: There were no severe adverse events, cardiotoxicity or neutropenia. Patients with negative estrogen or progesterone receptors, or high KI-67 suffered more alopecia, while HER2 overexpressing patients had less severe nausea. Conclusion: This pre-operative chemotherapy regimen was well tolerated on the whole; side-effect profiles were correlated with tumor biological factors and also with response.*

There is considerable interest in the relative benefits and risks of pre-operative chemotherapy *vs*. adjuvant chemotherapy in breast cancer. By down-staging the primary tumor, pre-operative therapy increases the proportion of patients eligible for breast-conserving therapy and thus contributes to quality of life. In an individual patient, the response of the primary tumor to pre-operative therapy could portend the response of possible systemic disease to subsequent (*e.g.* adjuvant) therapy (1-5); thus, "chemo-responsiveness" as a persistent individual attribute could thus eventually act as a marker to improve and individualize clinical therapy recommendations.

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However, it has not yet been possible to demonstrate a survival benefit of any chemotherapy regimen when administered in the pre-operative (neoadjuvant) rather than adjuvant setting: in randomized trials comparing the two settings, relapse-free and overall survival were comparable for a given chemotherapy regimen (6-8). In principle, the benefits of pre-operative therapy need to be weighed against the risks arising from delay of several months in primary surgery. Re-excision and local recurrence risk have also been key issues, though recent results (9) point to equivalent re-excision risks in the pre-operative and adjuvant settings: a systematic review (10) concluded that, while pre-operative therapy has been associated with risk of locoregional recurrence, increases do not occur provided the treatment concept includes surgery, even in case of complete remission.

As for the choice of pre-operative chemotherapy, much can be learned from experience in the adjuvant setting. Combination chemotherapy is generally considered to be more effective than monotherapy and is recommended by the NIH in most cases of primary breast tumors exceeding 1 cm in size (11, 12); there is strong evidence (13) that polychemotherapy including anthracyclines leads to better disease-free and overall survival than CMF. Adjuvant taxanes have improved overall survival (OS) in several studies (14, 15), in particular the GEICAM study (16, 17).

Although the combination of doxorubicin / paclitaxel has shown high efficacy, pre-operative breast cancer trials employing this combination have revealed a high risk of cardiotoxicity (18-21). The search for a correspondingly effective anthracycline-taxane polychemotherapy with lower toxicity has led to considerable interest in the combination of epirubicin with paclitaxel. The use of this combination in the current pre-operative setting was based on evidence of its efficacy in adjuvant as well as pre-operative trials and on a basic understanding of its chemotherapeutic action on the tumor (22-24). The anthracycline-based agent epirubicin (4'-epimer of doxorubicin) is less toxic than doxorubicin at the same dosage and is widely used in Germany for the treatment

of both primary and metastasized breast cancer, as well as for ovarian cancer and soft-tissue sarcoma (25). It is active during the S and G_2 cell cycle phases and interacts with DNA in a variety of different ways including intercalation, DNA strand breakage and inhibition with the enzyme topoisomerase II. While less intensive than doxorubicin (26), epirubicin's known side-effects include hematological and cardiac toxicity, as well as mucositis, nausea and vomiting, reversible hair loss and local skin reactions.

The taxane paclitaxel delays depolymerisation and promotes apoptosis. The side-effects of taxanes (24) generally include allergic reactions, bone marrow toxicity and cardiac toxicity, as well as possible cumulative liver complications such as neutropenia, leukopenia, thrombopenia and anemia. Neurological toxicity is also reported.

In view of the potential benefits of pre-operative chemotherapy in breast cancer, such as increased chance of breast-conserving surgery, it is important to quantify the risk of side-effects (depending on dosage and timing of treatment) and if possible to develop pro-active management strategies. In the case of dosage-limiting complications, such as hematological toxicity and cumulative cardiotoxicity, optimal risk assessment and management could benefit patient response (and ultimately survival) by minimizing the need to deviate from the planned chemotherapy schedule. This impact could be especially strong in the case of dose-dense schedules. Even in the case of less severe side-effects, improved quantification of risks and pro-active supportive care could impact patient quality of life quite strongly and also provide insights into the interaction of chemotherapeutic agents with the tumor. To this end, the present paper focuses on improving the ability to estimate risks of side-effects due to pre-operative epirubicin and paclitaxel chemotherapy in breast cancer using tumor biological factors.

Patients and Methods

This study was conducted at the OB/GYN department at Cologne University between 2000 and 2003 (27). Diagnosis of primary breast cancer was based on mammography, mammasonography, MRT and PET; 41 consecutive M0 patients satisfying eligibility requirements for treatment by combination pre-operative chemotherapy epirubicin and paclitaxel were initially included. Three patients were lost to follow-up for reasons unrelated to their disease stage or treatment, leaving a total of 38 for analysis, of whom 29 had ductal and 5 lobular carcinomas. Eleven patients received supporting Erypo® therapy. Median age was 49.7 years (30-69). Of the 33 patients reporting menopausal status, 17 were pre-menopausal and seven had received hysterectomies. Diagnostics for primary breast cancer included mammography, breast ultrasound and magnetic resonance imaging (MRI). Prior to chemotherapy, high-speed core biopsies were evaluated (blinded assessment) to determine HER2/NEU (DAKO-Test), Ki-67 and hormone receptor percentages (immunohistochemistry), as well as histology and differentiation.

The study protocol specified that patients should receive up to six cycles of epirubicin (intravenous one-hour infusion, 90 mg/m^2) and paclitaxel (175 mg/m^2) chemotherapy. Therapy response was evaluated every other cycle by clinical and sonographic tests; dose modification criteria were evidence of progression after two or four cycles. In this case, a new core biopsy was taken, chemosensitivity was determined, and a new chemotherapy regimen was determined. Disease characteristics of this collective have been previously described (27).

Blood counts were taken every week. At each chemotherapy cycle, patients received a check up including measurements of vital functions, differential blood count, Karnofsky index, and determination of chemotherapy-dependent toxicities. After completion of pre-operative therapy, patients who were considered appropriate candidates for breast conserving surgery were offered segmental mastectomy (lumpectomy). Patients who were considered inappropriate for breast-conserving surgery or who did not desire it underwent total mastectomy.

Statistical methods. Measurements of estrogen receptor (ER), progesterone receptor (PgR) and Ki-67 were modeled statistically as continuous, metric variables. Binary variables were introduced for alopecia, anemia and nausea.

Correlations between metric variables were computed as Spearman correlations. The Mann-Whitney test was performed to test associations between continuous and binary factors (*e.g.* Ki-67 as a predictor of hair loss). Fisher's exact test or Chi^2 tests were performed to test associations among categorical variables (*e.g.* HER2 amplification as a predictor of nausea). *P*-values <0.05 were reported as significant. Frequency confidence ranges and probability limits were reported using a non-informative prior.

Results

There were no treatment-related deaths or severe adverse events. In particular, there were no cases of clinical congestive heart failure or other recognizable cardiotoxicity. There were no cases of neutropenia in this study. With this number of patients, the estimated probability that the true frequency of one of these complications in the population exceeds 10% is less than 1.5%, and the probability that a true frequency exceeds 7.5% is less than 5%.

With the aid of epoetin alfa, anemia did not cause any deviations from the planned chemotherapy schedule. No significant association was found between anemia and any tumor biological factor, radiation, medication or previous medical history.

Table I summarizes chemotherapy received and frequencies of side-effects. Deviations from the chemotherapy protocol (for reasons other than anemia) occurred in 2/38 patients; 23/38 patients received 6 cycles, 5/38 received 5 cycles, 9/38 4 cycles, and 1/38 3 cycles.

Nausea (and vomiting) tended to increase up to the fourth cycle. Classifying patients according to most severe nausea experienced, 14 patients suffered nausea exceeding the level light, 19 light or none, 5 unknown. There was a highly significant (p=0.004) relationship between HER2/NEU over-expression and nausea, with 0/9 evaluated HER2$^+$ patients

Table I. *Chemotherapy cycles received and frequencies of side-effects.*

	N
Number of chemotherapy cycles	
6	23
5	5
4	9
3	1
Nausea and vomiting	
Moderate	14
Light or none	19
Unknown	5
Mucositis	
Present	7
Absent	23
Unknown	8
Alopecia	
Present (reversible)	18
Absent	13
Unknown	7

reporting nausea *vs*. 14/24 $HER2^-$ patients. Again, this relation is noteworthy in view of the positive association of $HER2^+$ status with response to chemotherapy in this collective.

Mucositis data were available for 30 patients. Of these, 7 patients had mucositis (2 of these only mild). There was a weak positive (borderline significant) correlation between mucositis severity and nausea.

Alopecia is a frequent and expected side-effect of this chemotherapy regimen. It was possible to reconstruct the alopecia time series in 31 out of 38 patients; by the fourth cycle, 18/31 patients reported complete (but reversible) alopecia. Classifying patients according to no/little hair loss *vs*. other categories (alopecia), a surprisingly clear relationship between alopecia and tumor biology emerges: Patients with more negative estrogen or progesterone receptor scores were more likely to suffer hair loss (ER: p=0.03; PgR: p=0.02), as were women with high proliferation marker (Ki-67: p=0.01). Note that ER and PgR were themselves positively correlated (R=0.505, p=0.001), and Ki-67 was negatively correlated with ER (R=–0.423, p=0.01) and with PgR (R=–0.425, p=0.01).

These associations are also noteworthy in view of similar associations of these markers with response to chemotherapy. In fact, alopecia itself was positively associated in this collective with a decrease in tumor size as measured by pathology (p=0.024).

Discussion

To the extent that the response to a pre-operative therapy regimen represents a surrogate endpoint for expected long-term survival, pre-operative trials provide a key source of evidence for optimization and individualization of future breast cancer treatment. However, for current primary breast cancer patients, the decision for or against pre-operative chemotherapy and the choice of regimen require weighing benefits against risks based on relevant, predictive individual characteristics (28).

To this end, it is necessary to quantify predictive factors not only for response in the pre-operative setting, but also for severity and risk of side-effects, as well as their dependence on dosage and scheduling and, if possible, to develop pro-active management strategies. In particular, estimates of side-effects for pre-operative administration of a chemotherapeutic regimen should ideally be based on evidence from that setting, rather than on studies in the adjuvant setting. In the case of dosage limiting complications, such as hematological toxicity and cumulative cardiotoxicity, optimal risk assessment and management could impact patient response by minimizing the need to deviate from the planned chemotherapy schedule. This impact could be especially strong in the case of dose-dense schedules. Even in the case of less severe side-effects, improved quantification of risks and pro-active supportive care could impact patient quality of life quite strongly.

Regarding the safety of pre-operative epirubicin (90 mg/m^2) and paclitaxel (175 mg/m^2) chemotherapy in the present study of 38 primary breast cancer patients, there were no severe adverse complications in particular involving hepatic, neurological or cardiac toxicity. Anemia was well controlled by epoetin alfa (29, 30). The 15/38 patients receiving fewer than the intended six cycles did so because of lack of response rather than side-effects.

The safety findings may be compared with dose limits of this combination in the metastatic breast cancer setting. In a previous study (31), epirubicin (50-60 mg/m^2) was followed by a 3-hour paclitaxel infusion (110-250 mg/m^2). Dose-limiting toxicity was reported at 60 mg/m^2 epirubicin and 200 mg/m^2 paclitaxel, with two out of three patients experiencing febrile neutropenia; in the combination epirubicin 50 mg/m^2 and paclitaxel 250 mg/m^2, febrile neutropenia occurred in 1/6 patients. Complications included neutropenia of grade 3 (37%) and grade 4 (19%) and neurotoxicity in 42%; cardiotoxicity occurred in 13%. In another study (32), paclitaxel was varied in 50 patients with epirubicin held fixed at 90 mg/m^2. There were no cardiac complications observed in the course of eight cycles. The dosage-limiting toxicity was febrile neutropenia, which occurred at 225 mg/m^2 paclitaxel in two patients and resulted in a recommendation of 90 mg/m^2 epirubicin and 200 mg/m^2 paclitaxel. In yet another study (20), 57 patients received one-hour infusions of 60 mg/m^2 epirubicin followed by a 3-hour paclitaxel infusion (175 mg/m^2). No cases of cardiotoxicity were found, while grade 3-4 neutropenia was observed in 72%, but no febrile neutropenia. Bellino *et al*. (33) studied 48 metastatic patients, 37 of whom had previously received at least 12 months of

adjuvant chemotherapy, 7 of these with anthracyclines. Every three weeks, patients received 60-90 mg/m^2 epirubicin on the first day 175-200 mg/m^2 paclitaxel on the second day. Grade 3-4 neutropenia was observed in about half of the patients. Peripheral neuropathology occurred at grade 1-2 in 36 patients and at grade 3-4 in 2 patients. One patient left the study due to neurotoxicity. There were no cases of cardiotoxicity. In one final study (34), epirubicin/paclitaxel (60 mg/m^2; 175 mg/m^2) and epirubicin/cyclophosphamide (60 mg/m^2, 600 mg/m^2) were compared (n=560) in advanced metastatic breast cancer: fewer side-effects occurred with the epirubicin / paclitaxel regimen, with equal survival. A similar comparison of 705 patients found more side-effects in the epirubicin/ cyclophosphamide arm (but also better response) (35).

In the adjuvant setting (36), the combination epirubicin/ paclitaxel was given in a two-day schedule every three weeks (day 1: epirubicin 90 mg/m^2 6 h by infusion, day 2: paclitaxel 220 mg/m^2, 3 h by infusion). Stage 3 patients received a maximum of 6 cycles, while stage 4 patients received up to 8 cycles. Mild to moderate neurotoxicity was observed in some patients. Only 2 patients (8%) had grade 4 neutropenia, none had febrile neutropenia. Neither acute cardiotoxicity nor other heart abnormalities were observed.

In a randomized pre-operative study (37), dose dense sequential therapy (3x epirubicin 150 mg/m^2 followed by 3x paclitaxel 250 mg/m^2 every 2 weeks with G-CSF) was compared to a standard dose (4x ET (90 mg/m^2; 175 mg/m^2) every three weeks. Dose-dense sequential therapy led to a higher thrombopenia rate, but also more pCR and breast conserving surgery.

In the present study, pathological complete remission occurred in 6 out of 36 patients (2 missing); median sonographically determined tumor reduction was about half; tumor stage and nodal status also improved. Breast-conserving surgery was carried out in 24/38 patients. As reported in (27), all measures of response were correlated with negative hormone receptors (ER and PgR) as well as with proliferation (Ki-67).

The body's reaction to chemotherapy reflects interactions both with tumor biology and with normal processes. Although the goal of chemotherapy is tumor remission, remission is not the only response to therapy. The processes that lead to remission could conceivably have other physiological consequences that can be quantified. Hence, in an effort to learn as much as possible from the data, possible relationships between tumor biology and side-effects that are revealed in this data have been studied. This impact could be especially strong in the case of dose-dense schedules.

No significant association was found between anemia and any tumor biological factor, radiation, medication or previous medical history. Nonetheless, remarkably clear relationships between tumor biology and other side-effects have emerged from this study: patients with lower ER or PgR values were more likely to suffer from at least moderate alopecia, as were women with high proliferation marker Ki-67. Notably, these markers are associated in a similar way with response (27) to pre-operative chemotherapy. In fact, alopecia is itself positively associated with decrease in tumor size. Furthermore, there was a highly significant association between HER2/NEU amplification and (lack of) nausea. Again, this relation seems worth mentioning in view of the positive association of HER2$^+$ status with response (27). These associations, while of course only preliminary, raise the question of whether the side-effects of epirubicin/paclitaxel chemotherapy are simply a direct consequence of their effects on the whole body, including non-malignant cells, or whether interactions of chemotherapeutic agents with each other and with tumor biology might activate processes that impact the patient's side-effect profile. It would seem advisable to check these associations (retrospectively or prospectively) in independent pre-operative study data with larger patient numbers.

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