



## Cardiac sequelae of doxorubicin and paclitaxel as induction chemotherapy prior to high-dose chemotherapy and peripheral blood progenitor cell transplantation in women with high-risk primary or metastatic breast cancer

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### Summary:

Doxorubicin plus paclitaxel has been shown to be an active regimen for metastatic breast cancer and is now frequently used as adjuvant therapy for high-risk primary breast cancer. Initial studies reported a higher than expected rate of cardiac toxicity with this regimen. We studied 105 patients with either high-risk primary breast cancer or metastatic breast cancer who were treated with doxorubicin (60 mg/m<sup>2</sup>) and 3-h infusions of paclitaxel (175 mg/m<sup>2</sup>) cycled every 3 weeks. Patients received three cycles of chemotherapy for high-risk primary or four cycles for metastatic disease. Patients then proceeded to high-dose chemotherapy (HDC) (STAMP I cyclophosphamide, cisplatin and carmustine) and peripheral blood progenitor cell transplantation (PBPC). Patients underwent radionuclide multi-gated angiograms (MUGA) before and following induction chemotherapy and following HDC. During induction chemotherapy 40 (38%) of the patients had a reduction in left ventricular ejection fraction (LVEF). Fourteen had a decrease of 20% or greater and two were mildly symptomatic from CHF. There was additional reduction in the LVEF after HDC with a median value for LVEF of 59% (range, 20–78%). During HDC 10 patients developed clinical signs of congestive heart failure (CHF). Five patients responded to diuretic therapy and did not require any additional treatment. Four patients responded to vasodilation and/or digoxin with improvement in cardiac function. A clinically significant decrease in cardiac function was found in a small number of patients after induction chemotherapy and HDC with PBPC. The majority of the patients tolerated this regimen without problems. Although there was a decline in LVEF as measured by radionuclide MUGA this did not prevent the majority of patients from proceeding with HDC. *Bone Marrow Transplantation* (2000) 25, 1047–1052.

**Keywords:** autologous; transplantation; breast cancer; doxorubicin; cardiotoxicity

A previous study of the combination of doxorubicin, 5-fluorouracil and methotrexate as an induction regimen prior to HDC and PBPC showed significant activity with a CR rate of 23% and a PR rate of 46% for an overall response of 72% in women with metastatic breast cancer.<sup>1</sup> While the regimen showed very good activity it also had a significant toxicity profile with mucositis being a major drawback. As a consequence we were eager to define an alternative induction regimen for use in our next generation trials of HDC with hematopoietic cell support. Paclitaxel (Taxol; Bristol-Meyers Squibb, Princeton, NJ, USA) was the initial taxane evaluated in the treatment of metastatic breast cancer. It was found to be an active agent both in patients who were chemotherapy naive and in those who were anthracycline-resistant.<sup>2,3</sup> The significant activity of paclitaxel plus the established role of doxorubicin in breast cancer, led to the logical choice of the combination of these two agents as an induction regimen.<sup>4–7</sup> Gianni and coworkers<sup>8</sup> first reported the combination of doxorubicin and a 3-h infusion of paclitaxel in 1995. They established that a significant number of women (94%) with previously untreated metastatic breast cancer responded to this combination. Unfortunately, a higher number of patients in this and subsequent studies developed cardiac arrhythmia and congestive heart failure at doxorubicin doses lower than previously reported for doxorubicin alone.<sup>9,10</sup>

Combinations of paclitaxel with other agents have indicated that the sequence and infusion rates of the respective agents have a significant effect on the maximum tolerated dose (MTD). When paclitaxel, doxorubicin and cyclophosphamide were given in a sequential fashion rather than concurrently no increase in cardiac toxicity was observed.<sup>11</sup> Studies employing longer infusions of both paclitaxel and doxorubicin found a sequence-dependent difference in the dose-limiting toxicity.<sup>12</sup> With a short infusion of doxorubicin and a 3-h infusion of paclitaxel the MTD did not appear to be affected by the drug sequence.<sup>8</sup> Pharmacokinetic companion studies of this combination demonstrated

an effect of paclitaxel on the nonlinear disposition of doxorubicin and its metabolite doxorubicinol.<sup>13</sup>

We were interested in evaluating this combination as induction chemotherapy for patients with either metastatic or high-risk primary breast cancer before HDC and PBPCT. High-dose cyclophosphamide is known to be potentially cardiotoxic and the physiologic stress of HDC raised concerns about the potentially synergistic cardiac toxicity with doxorubicin and paclitaxel. We, therefore, evaluated the effect of doxorubicin and paclitaxel on cardiac function before and after induction chemotherapy and following HDC and stem cell transplantation.

## Patients and methods

### Patients

From January 1996 to April 1998 105 patients with either high-risk primary breast cancer stage II/III or stage IV metastatic breast cancer were enrolled into three clinical trials of doxorubicin and paclitaxel chemotherapy followed by HDC with autologous peripheral blood progenitor cell transplantation (PBPCT). Inclusion criteria were as follows: good performance status (0–2), adequate bone marrow function (absolute neutrophil count  $\geq 2000/\mu\text{l}$  and platelet count  $\geq 100\,000/\mu\text{l}$ ), normal liver function (bilirubin level  $\leq 1.25$  times upper normal limit) and renal function (creatinine  $\leq 1.25$  times upper normal limit). Left ventricular ejection fraction (LVEF) was assessed by radionuclide MUGA and had to be  $\geq 50\%$ . One patient with a pretreatment LVEF of  $< 50\%$  had exercise echocardiogram with exercise augmentation in LVEF and was included in the trial. Patients previously treated with doxorubicin were accepted if they had a cumulative dose of less than  $300\text{ mg/m}^2$ . The Institutional Review Board and Comprehensive Cancer Center Clinical Trial committee of Wayne State University approved all trials. All patients signed informed consent for these studies.

### Treatment plan

The dose of doxorubicin was fixed at  $60\text{ mg/m}^2$  and was administered as a 5-min infusion before the start of paclitaxel. Paclitaxel was diluted in 5% dextrose and filtered through a  $22\text{ }\mu\text{m}$  inline filter. The dose of paclitaxel was  $175\text{ mg/m}^2$  administered as a 3-h infusion. Patients were premedicated with dexamethasone 20 mg orally 12 and 6 h before chemotherapy. Immediately prior to the chemotherapy patients received dexamethasone 20 mg i.v., diphenhydramine 50 mg i.v. and cimetidine 300 mg i.v. The chemotherapy was administered every 21 days. Patients received filgrastim (Neupogen; Amgen, Thousand Oaks, CA, USA) after chemotherapy if they developed neutropenia during their first cycle or subsequent cycles of chemotherapy at the discretion of the attending physician. The referring clinical oncologist administered all chemotherapy.

Patients with stage II or III disease received three cycles of doxorubicin and paclitaxel. These patients then proceeded to HDC and PBPCT. Patients with metastatic dis-

ease received four cycles of doxorubicin and paclitaxel. Patients were evaluated for response and then proceeded to PBPC mobilization, collection and then to HDC and PBPCT.

PBPCs were mobilized with filgrastim ( $10\text{ }\mu\text{g/kg/day}$ ) for 5 days. PBPC collections were performed using a Baxter 3000CS (Baxter Therapeutic, Deerfield, IL, USA). A target of  $5.0 \times 10^6$  CD34<sup>+</sup> cells/kg and a minimum of  $2.5 \times 10^6$  CD34<sup>+</sup> cells/kg were required before HDC. Patients who did not have an adequate PBPC collection with filgrastim alone underwent a second PBPC mobilization. Patients received paclitaxel  $175\text{ mg/m}^2$  as a 24-h infusion followed by cyclophosphamide  $2\text{ g/m}^2$  as a 1-h infusion. Patients received MESNA uroprophylaxis  $2\text{ g/m}^2$  divided into three doses given immediately before and 4 and 8 h after cyclophosphamide in addition to i.v. and oral hydration.

### High-dose chemotherapy and PBPC transplantation

The HDC consisted of cyclophosphamide  $1875\text{ mg/m}^2$  given daily as a 1-h infusion on days –6, –5, –4; cisplatin  $55\text{ mg/m}^2/\text{day}$  continuous i.v. infusion days –6, –5, –4 and carmustine  $600\text{ mg/m}^2$  as a 2-h infusion on day –3. Patients received vigorous i.v. hydration at  $200\text{ ml/m}^2/\text{h}$  and continuous bladder irrigation.

### Cardiac monitoring

Patients underwent radionuclide MUGA cardiac blood scan for LVEF before initiation of chemotherapy, after the second cycle of doxorubicin and paclitaxel, at the conclusion of induction chemotherapy and 42 days following the HDC with PBPCT. The time points in the results were following the completion of the induction chemotherapy and 42 days following the PBPCT. A 2-D echocardiogram with exercise was performed in patients with radionuclide MUGA less than 50%. During the HDC patients had a daily ECG before each dose of cyclophosphamide. Cardiac toxicity was graded according to the NCI/CTEP common toxicity criteria. Grade 0  $\leq 5\%$  decrease in LVEF, grade I loss of  $\geq 5\%$  but  $\leq 20\%$ , grade II loss of  $\geq 20\%$ , grade III mildly symptomatic but responsive to therapy and grade IV severe or refractory CHF.

### Statistical analysis

Groups were compared by the  $\chi^2$  test and correlations were estimated by the Spearman rank test. Logistic regression was used to analyze the predictive value of the different variables on the risk of clinically significant cardiac toxicity (grade III or IV) during HDC. Variables were analyzed in a forward stepwise manner, with a two-sided significance level of  $P = 0.05$  for the likelihood ratio test used as the criterion for including a covariant in the model. Results are presented as risk ratios.

## Results

### Patients and treatment

From January 1996 to April 1998, 105 patients with stages II, III or IV breast cancer were included in this study. Patient characteristics are shown in Table 1. The group had a median age of 47 years and a median SWOG performance of 0. Twenty-five patients had received prior doxorubicin-based chemotherapy as adjuvant chemotherapy. Patients received a median of four cycles of the doxorubicin/paclitaxel combination (range 2–6), which represented an average dose of 240 mg/m<sup>2</sup> (range 90–540 mg/m<sup>2</sup>). Nine patients received additional cycles of induction chemotherapy because of insurance approval delays. Five patients did not continue to high-dose chemotherapy and PBPCT because of progressive disease during induction chemotherapy. Two patients with LVEF of less than 50% were asymptomatic. They had an echocardiogram with increased LVEF during exercise and continued to PBPCT. One of these patients did not receive carmustine during the HDC because of left ventricular dysfunction.

Eight patients did not have a follow-up MUGA scan at their day 42 evaluation. One died of disease progression without a repeat MUGA and a second had neurologic complications and also did not have a day 42 MUGA. The six other patients did not have a MUGA scan at their day 42 evaluation, but were asymptomatic of cardiac disease and had no clinical signs of CHF at evaluation.

### Cardiac sequelae

Myocardial contractility was evaluated as described in the Methods section. The baseline median LVEF was 66% (range, 49–88%) and decreased to 63.5% (range, 41–82%) following induction chemotherapy. The cumulative dose of doxorubicin inversely correlated with LVEF ( $R = -0.23$ ,  $P < 0.005$ ) (Figure 1). The decrease in LVEF was significantly larger if the patient had received prior radiotherapy to the chest wall ( $P < 0.05$ ). Forty-nine of the 105 (46.7%) patients had a reduction of LVEF during the induction chemotherapy. In 14 (13%) of the patients the reduction was greater than 20% from baseline, ie grade II cardiac toxicity. Two of the patients had a decrease in LVEF of greater than 20% and were mildly symptomatic, ie grade III cardiac toxicity.

After a median total cumulative dose of 285 mg/m<sup>2</sup> of

doxorubicin, 50% of the patients lost at least 10% of their LVEF compared with the baseline value. Fifty-six per cent of patients who had received prior adjuvant radiation therapy had a 10% reduction in their LVEF. In this group the median total cumulative dose of doxorubicin was only 240 mg/m<sup>2</sup>. The incidence of a 10% reduction in LVEF during induction chemotherapy was statistically significantly higher in the group with prior radiation therapy ( $P < 0.05$ ).

Table 2 summarizes the sequential change in the LVEF during induction chemotherapy and following HDC and PBPCT. An additional reduction in the median LVEF was observed after HDC. The median LVEF after HDC and PBPCT was 59% (range, 20–78%). In the 10 patients who developed signs of cardiac toxicity during HDC there was a significantly greater decrease in the LVEF than in the patients who did not develop signs of CHF. A greater reduction in the post induction chemotherapy LVEF was observed in patients previously treated with anthracyclines or who received radiation therapy as adjuvant therapy.

Table 3 lists the resultant cardiac function according to the National Cancer Institute common toxicity criteria (CTC). Only two patients had grade III cardiac toxicity during induction treatment. One patient was not transplanted because of cardiac deterioration during induction chemotherapy. The second patient with grade III toxicity had an exercise echocardiogram with an increase in LVEF with exercise and proceeded to HDC and PBPCT. During HDC 10 patients developed symptoms and signs of cardiac failure and met the criteria for grade III or IV cardiac toxicity. Characteristics of the 10 patients who developed CHF during HDC are listed in Table 4. Five patients developed signs of CHF during the HDC and responded to fluid restriction and diuretic therapy. These patients required no additional treatment and are currently requiring no therapy for cardiac dysfunction. One patient died during the immediate post-transplant period of sepsis and CHF. Four patients responded to vasodilator therapy and/or digoxin with improvement in cardiac function. At present three patients continue to require cardiac medications.

### Multivariate analysis

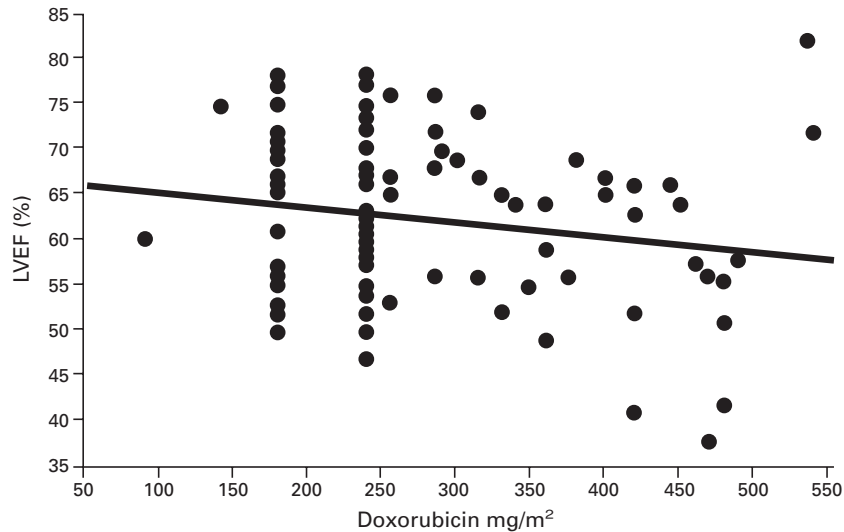
A logistic regression analysis for the development of grade III or IV cardiac toxicity was performed for 100 patients who completed HDC. Factors analyzed were age, dose of doxorubicin both during induction and total, prior radiotherapy to the left thorax, PBPC mobilization with a cyclophosphamide-containing regimen, pre-treatment LVEF, post-induction LVEF, and percentage loss of LVEF. As shown in Table 5, age greater than 50, dose  $\geq 240$  mg/m<sup>2</sup> of doxorubicin during induction, mobilization with cyclophosphamide, and basal LVEF less than 55% were predictive of overall cardiac toxicity during HDC and PBPCT (Table 5).

### Response to doxorubicin and paclitaxel

Seventy-three patients with metastatic disease were evaluable for response to the induction chemotherapy. All patients completed four cycles of chemotherapy including those who had progressive disease. The overall response

**Table 1** Patient's characteristics

No. of patients	105
Median age (range)	47 (23–65)
Stage:	
II	24 (23%)
III	8 (7%)
IV	73 (70%)
Prior adjuvant chemotherapy (%)	
Overall	47 (46%)
Doxorubicin based	18 (17%)
CMF	21 (21%)
Sequential doxorubicin/CMF	8 (7%)
Prior radiotherapy of left thorax	16 (15%)



**Figure 1** LVEF at following doxorubicin and paclitaxel induction chemotherapy vs total cumulative doxorubicin (included adjuvant therapy) mg/m<sup>2</sup>.

**Table 2** Evolution of LVEF (median and range)

	Basal	After induction <sup>a</sup>	After PBPCT <sup>b</sup>	Total doxorubicin
Overall	66 (49–87)	63.5 (41–82)	60 (20–78)	240 (90–540)
Patients with toxicity	65 (52–73)	53 (38–82)	48 (20–66)	255 (180–540)
No toxicity	66 (49–87)	63 (47–82)	61 (43–78)	240 (90–480)
<i>P</i>	NS	0.012	0.003	NS
Prior doxorubicin	64.5 (49–82)	58 (41–82)	57 (20–72)	
No prior doxorubicin	66 (51–85)	65 (47–78)	60 (30–78)	
<i>P</i>	NS	0.049	0.024	
Prior radiotherapy	64.5 (49–85)	56 (41–75)	60 (44–76)	
No prior radiotherapy	66 (51–82)	64.5 (42–82)	60 (20–78)	
<i>P</i>	NS	0.029	NS	

<sup>a</sup> Following the last cycle of induction chemotherapy.

<sup>b</sup> Six weeks from the day of PBPCT.

**Table 3** Cardiac toxicity according to the Common Toxicity Criteria<sup>a</sup> after both induction and high-dose chemotherapy and PBPCT

Grade	After induction	After PBPCT
0	56 (53.3%)	41 (45%)
I	33 (31.4%)	28 (30%)
II	14 (13%)	14 (13%)
III	2 (2%)	9 (9%)
IV	0	1 (1%)
Overall	105	92 <sup>b</sup>

<sup>a</sup>Common toxicity criteria: grade 0 loss of ≤5% LVEF, grade I loss of more than 5% but less than 20% of LVEF, II loss of more than 20%, grade III mild symptomatic responsive to therapy, and grade IV severe or refractory CHF.

<sup>b</sup>Five patients did not receive high-dose chemotherapy because of disease progression, two patients died shortly after treatment and LVEF was not evaluated at day 42 post HDC, none of them had grade III toxicity during BMT, six patients did not have post HDC MUGA but all were asymptomatic.

was 63% with 16 (22%) CRs and 30 (41%) PRs. Eighteen (25%) had progressive disease and nine (12%) had SD. No patients with either stage II or III developed metastatic disease during the induction chemotherapy.

## Discussion

We have reported the cardiac effects of doxorubicin and paclitaxel chemotherapy regimen for both metastatic and high-risk primary breast cancer before HDC and PBPCT. This regimen was similar to that of Gianni and coworkers<sup>8</sup> with doxorubicin followed by a 3-h infusion of paclitaxel.

In the present study, 50% of patients receiving a cumulative dose of doxorubicin ≥285 mg/m<sup>2</sup> had at least a 10% reduction in LVEF. Despite this reduction in LVEF the dose of doxorubicin was not a predictive factor in the development of CHF during the high-dose chemotherapy. Our results on the combination of doxorubicin and paclitaxel are similar to the cardiotoxicity initially reported by Gianni *et al.*<sup>8</sup> In that study, previously chemotherapy naive women

**Table 4** Relevant characteristics of the 11 patients who developed clinical cardiac failure

Age	Prior hypertension	Chest wall radiotherapy	Cytoxin PBPC mobilization	Total doxorubicin mg/m <sup>2</sup>	LVEF			Clinical
					Basal	Induction	PBPCT	
56	Yes	No	Yes	330	73	52	20	Death during HDC
53	No	Yes	No	255	55	53	66	Fluid overload, presently receiving no therapy
53	No	No	Yes	480	53	42	53	Fluid overload, presently receiving no therapy
55	No	Yes	Yes	470	61	47	56	BCNU stopped because LVD
54	No	No	Yes	240	65	66	58	Fluid overload, presently receiving no therapy
36	Yes	No	No	240	69	55	30	Presently mild LVD
53	Yes	No	Yes	255	70	65	45	Presently mild LVD
50	No	No	Yes	240	68	61	50	SV tachycardia and LVD, presently receiving treatment
48	No	No	Yes	240	57	62	50	Fluid overload, presently receiving no therapy
65	No	Yes	Yes	180	63	53	44	Fluid overload

LVD = left ventricular dysfunction; SV = supraventricular.

**Table 5** Multivariate analysis

Factor	Risk	Standard error	P
Age (<50 vs ≥50)	7.0	0.93	0.02
Baseline LVEF	15.5	0.42	0.07
Cy as mobilization	19.7	1.22	<0.01
Doxorubicin (<240, ≥240)	9.0	1.41	0.06

Stage, radiotherapy to left chest and LVEF post induction therapy were not significant.

with metastatic breast cancer received between one and eight cycles of doxorubicin with a 3-h infusion of paclitaxel. Thirty-one of 33 of the evaluable patients showed a decrease in LVEF and six women developed symptomatic congestive heart failure after a median dose of 480 mg/m<sup>2</sup>.

Both of these results are different from those reported by The Eastern Cooperative Oncology Group who treated patients with metastatic breast cancer with the combination of doxorubicin and paclitaxel.<sup>6</sup> Patients were randomized to either single agent doxorubicin or paclitaxel or combination doxorubicin and paclitaxel. The combination of doxorubicin/paclitaxel was not found to have excessive cardiac toxicity and the overall response to the combination was better than single agent therapy.<sup>4,6</sup> In that study, patients received doxorubicin 50 mg/m<sup>2</sup> by intravenous push, followed 4 h later by paclitaxel 150 mg/m<sup>2</sup> by continuous 24-h infusion. The lower incidence of cardiotoxicity may relate to the delay in the administration of the paclitaxel following the doxorubicin infusion.

High-dose cyclophosphamide can also cause myocardial toxicity. It is the dose-limiting toxicity when used in regimens with hematopoietic cell support.<sup>14-18</sup> The incidence of cardiac toxicity associated with bone marrow transplantation has been reported to vary between 2 and 9%. The incidence of grade III cardiac toxicity in patients undergoing HDC in our study was 11 of 100 (11%). The majority of the patients responded to diuretic therapy and had no additional cardiac problems during the PBPCT.

Pretransplant cardiac evaluation has not been found to correlate well with the risk of developing cardiac toxicity during transplantation, although there may be a higher incidence of cardiac toxicity for patients with EF less than 50%.<sup>19,20</sup> Previous reports on the predictive value of pre-transplant cardiac evaluation did not look at the effect of induction chemotherapy. In our series we found patients greater than 50 years of age, a pre-induction LVEF less than 55% or a loss of LVEF of 20% during induction chemotherapy were at greatest risk of developing clinically significant cardiac problems during HDC. We also found that patients who received PBPC mobilization with cyclophosphamide had a higher frequency of cardiac problems during the transplantation.

The current study has demonstrated that the combination of doxorubicin and paclitaxel is a highly active induction chemotherapy regimen when used as part of a HDC and PBPCT strategy. The major toxicity of cardiac injury appears, in large measure, manageable and largely avoidable particularly if attention is paid to patient age, baseline cardiac function, pre-transplant ejection fraction, cumulative dose of doxorubicin and attempting to minimize high-dose cyclophosphamide chemo-mobilization. This latter consideration may be facilitated by the use of novel mobilizing growth factors such as stem cell factor. The increasing use of adjuvant anthracyclines emphasizes the need for careful monitoring of total anthracycline dose.

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