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Decline in pulmonary function in patients with breast cancer receiving dose-dense chemotherapy: a prospective study

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Background: Prompted by complaints of dyspnea in breast cancer patients receiving adjuvant dose-dense chemotherapy (DDC), we sought to evaluate the possible association of DDC with pulmonary dysfunction.
Patients and methods: A total of 34 consecutive patients receiving adjuvant DDC were enrolled. The chemotherapy regimen consisted of i.v. doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) every 14 days ×4 with growth factor support followed by weekly i.v. paclitaxel 80 mg/m^2 ×12. The following parameters were prospectively measured before and after the AC protocol (P1, P2) and at completion of paclitaxel treatment (P3): presence of dyspnea, blood pressure, pulse rate, hemoglobin, erythrocyte sedimentation rate, C-reactive protein level, cardiac ejection fraction, and pulmonary function. Repeated measures analysis was used to evaluate differences among the time points, and paired *t*-test was used to evaluate differences between consecutive time points.
Results: Although only five patients (15%) complained of dyspnea, there was a significant decrease in mean carbon monoxide diffusing capacity (DLCO), in all patients from P1 (22.09 ml/min/mmHg) to P3 (15 ml/min/mmHg) and in 29 of 32 patients (90.6%) from P1 to P2 (15.96 ml/min/mmHg) ($P < 0.001$).
Conclusions: DDC is associated with a statistical significant reduction in DLCO. Awareness of this potential toxicity may be important in women with preexisting lung disease.
Key words: breast cancer, CRP pulmonary function, DLCO, dose-dense chemotherapy, ESR

introduction

As we improve the outcomes of patients with breast cancer, the long-term toxicity of various regimens becomes of paramount importance. Anthracyclines and taxanes are considered two of the most potent agents in the adjuvant treatment of breast cancer and their use is supported by the meta-analysis reported by the Early Breast Cancer Trialists' Collaborative Group [1, 2]. After showing an improvement in survival, dose-dense doxorubicin–cyclophosphamide followed by a taxane has been widely used, especially for patients with node-positive disease [3], with a beneficial effect on patient survival. Although dose-dense chemotherapy (DDC) is generally well tolerated, we observed that some women developed significant dyspnea that persisted after treatment completion. An in-depth examination of these patients to identify possible causes, such as anemia, cardiovascular disease, and pulmonary injury, disclosed that a decrease in pulmonary diffusion capacity was the only pathological finding. We therefore conducted a prospective study to systematically evaluate the possible association of DDC with pulmonary dysfunction. To our knowledge, this is the first study to describe changes in pulmonary function during DDC in patients with breast cancer.

patients and methods

The study group consisted of 34 consecutive patients with breast cancer who were receiving adjuvant DDC at the Institute of Oncology, Davidoff Center of Rabin Medical Center, in accordance with departmental guidelines, from September 2006 to April 2007. Patients with any known pulmonary illness were excluded. Baseline chest X-ray film or computed tomography scan before treatment was normal in all enrolled cases. DDC consisted of i.v. doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) ×4 every 14 days with granulocyte colony-stimulating factor (G-CSF) support, followed by weekly i.v. paclitaxel 80 mg/m^2 ×12. Dexamethasone 20 mg and i.v. H2 blocker were administered 30 min before each paclitaxel cycle. After 4 weeks, the steroid dosage was gradually decreased; cycles 8–12 of paclitaxel were given without the addition of steroids.

The following parameters were prospectively evaluated before and after the AC protocol (P1, P2) and again at the end of paclitaxel treatment (P3): physical examination, presence of dyspnea, blood pressure, pulse rate, hemoglobin level, erythrocyte sedimentation rate (ESR), C-reactive protein

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(CRP) level, cardiac ejection fraction by multiple-gated acquisition scan or echo and full pulmonary function tests, including spirometry, lung volume, and carbon monoxide diffusion capacity (DLCO, adjusted to hemoglobin levels). Pulmonary function tests were carried out at the same laboratory for all time points.

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. All participants signed an informed consent form before enrollment.

statistical analysis

Data were expressed as mean ± standard deviation or proportions, as appropriate.

Repeated measures analysis was used to evaluate differences in the study parameters among the three time points, to determine the overall change, and paired Student *t*-test was used to evaluate differences between consecutive time points. We also used a means graph to show the differences in DLCO over time. The percentage of the count of cases in which DLCO dropped over time was calculated, and binomial test was used to determine the significance of the reduction.

All analyses were carried out using SPSS 14 software (SPSS Inc, Chicago, IL).

results

Thirty-four patients were recruited to the study. Median age of the study group was 51.5 years (range 28–71), and median body surface area was 1.68 m^2 (range 1.48–2.04). Four patients presented with very high-risk stage I disease, 21 with stage II disease, and nine with stage III. Eleven patients (33%) had a negative estrogen receptor status. All patients had a performance status of zero, although 17 had other chronic morbidities that required treatment: eight hypertension, five diabetes mellitus (non insulin dependent), three hypothyroidism, and one stable and controlled atrial fibrillation. Women with Her-2Neu-positive disease were treated with trastuzumab concomitantly with paclitaxel and thereafter for up to 1 year.

Five patients (15%) complained of grade 1 dyspnea during their chemotherapy treatment or at follow-up. However, all 34 demonstrated a significant decrease in DLCO from P1 (mean, 22.09 ml/min/mmHg) to P3 (mean, 15 ml/min/mmHg), and 29 of 32 patients (90.6%) demonstrated a significant decrease in DLCO from P1 (mean, 22.09 ml/min/mmHg) to P2 (mean, 15.96 ml/min/mmHg) ($P < 0.001$)(Table 1). At P1, all patients had a DLCO above 70% and 82% tested above 80% of the predicted value, whereas in P3 only 54% and 14% of the patients achieved this result, respectively (figure 1). All values were corrected for hemoglobin. No significant changes in expiration–forced vital capacity ($P = 0.37$) or forced expiratory volume 1 ($P = 0.31$) (Table 2). Neither age nor smoking correlated with these changes. Cardiac function remained unchanged ($P = 0.54$).

Significant changes were noted in all three serum measured parameters (hemoglobin, ESR, and CRP). The details are shown in Table 3. Hemoglobin levels decreased throughout treatment ($P < 0.001$), mainly from P1 (13.35 g/dl) to P2 (11.6 g/dl) and then stabilized by P3 (11.6 g/dl). ESR increased, peaking at P2 (42.2 mm/h), and then decreasing by P3 (33.6 mm/h) ($P < 0.001$). CRP levels increased gradually from P1 (0.25 mg/dl) to P3 (1.55 mg/dl) ($P = 0.024$).

There were no significant changes in vital signs during treatment (Table 4).

discussion

Several chemotherapy agents are known to induce pulmonary toxicity but this has not been systematically assessed for most of the current adjuvant protocols being used extensively for breast cancer. Our study revealed a significant reduction in DLCO in all patients in the study. The major changes occurred during AC portion of the treatment, that is the doxorubicin + cyclophosphamide regimen with G-CSF support.

It is difficult to determine which of these agents was the most responsible for the toxicity. Bhalla et al. [4] reported that the traditional cyclophosphamide/doxorubicin/5-fluorouracil protocol was associated with a significant 12.6% decrease in mean DLCO which was not accompanied by other pulmonary symptoms. This reduction is lower than that observed in the present study. Doxorubicin alone has not been related to lung toxicity, although it was suspected in one report of life-threatening respiratory failure when given with G-CSF support [5]. Azoulay et al. summarized 84 published cases of pulmonary toxicity apparently associated with G-CSF treatment, including two involving G-CSF alone. They found that adult respiratory distress syndrome developed in nine patients during recovery from neutropenia enhanced by G-CSF. In addition, 73 patients experienced an exacerbation of chemotherapy-related pulmonary toxicity with the addition of G-CSF [6]. Cyclophosphamide can rarely cause pulmonary

Table 1. Statistical analysis of changes in DLCO between time points

DLCO	Paired differences					Significance (two tailed)
	Mean (ml/min/mmHg)	Standard deviation	Standard error mean	95% confidence interval of the difference		
				Lower	Upper	
Point 1–2	6.32	4.84	0.85	4.58	8.06	0.000
Point 1–3	7.16	3.34	0.62	5.89	8.44	0.000
Point 2–3	0.97	3.84	0.73	−0.52	2.46	0.193

DLCO, carbon monoxide diffusing capacity; P1—measurement before AC protocol; P2—measurement after AC protocol; P3–measurement at the end of paclitaxel treatment.

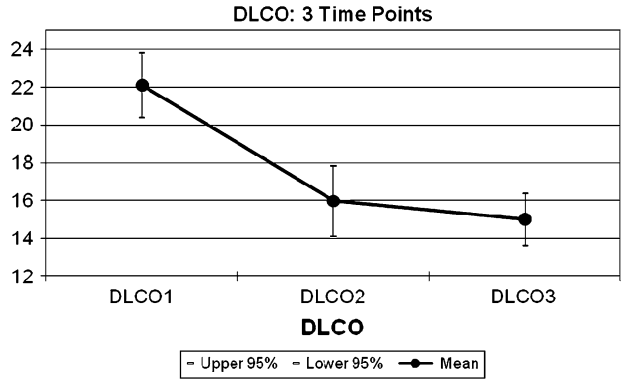

Figure 1. Change in carbon monoxide diffusing capacity (DLCO) at each time point. *P**—change in DLCO (ml/min/mmHg) from P1 to P2; *P***—change in DLCO (ml/min/mmHg) from P2 to P3. Note: P1—measurement before AC protocol; P2—measurement after AC protocol; P3—measurement at the end of paclitaxel treatment.

Table 2. Lung function values during DDC

Spirometry	*n*	Mean (liter)	Standard deviation	*P* value
FVC(exp) P1	33	3.13	0.68	
FVC(exp) P2	33	3.09	0.613	
FVC(exp) P3	29	3.12	0.65	0.196
FEV1 P1	33	2.68	0.64	
FEV1 P2	33	2.62	0.63	
FEV1 P3	29	2.64	0.65	0.306

DDC, dose-dense chemotherapy; FVC, forced vital capacity in liters; exp, expiration; P1, measurements before AC protocol; P2, measurements after AC protocol; P3, measurements at the end of paclitaxel treatment; FEV, forced expiratory volume in liters.

toxic effects such as interstitial pneumonitis and even fatal fibrosis more frequent when given in high dose [7–9].

Recently, a 17% rate of grade 3 and/or 4 dyspnea was observed in a phase II trial of weekly paclitaxel, given in a dose-dense schedule to patients with small-cell lung cancer [10]. Earlier studies reported severe taxane-related pulmonary toxic effects, such as pulmonary infiltrates and hypersensitivity reactions [11–13].

In the present study, fewer than 10% of the patients showed a further decrease in DLCO following paclitaxel therapy (P3), and there was no statistically significant reduction in diffusion capacity from P2 (following four cycles of AC) to P3 (completion of paclitaxel treatment), indicating that it was probably the combination of doxorubicin/cyclophosphamide and G-CSF that accounted for the pulmonary toxicity. Other factors such as age, weight, smoking history, chronic lung diseases, menstruation cycle, and decrease in hemoglobin can influence the DLCO results [14–16]. We therefore corrected for hemoglobin level in our analysis, and on multivariate analysis, neither age nor smoking history was found to have a statistically significant impact on pulmonary outcome.

None of the phase III adjuvant DDC trials in patients with breast cancer have reported lung toxicity [3, 17, 18]. One could

Table 3. Blood parameters during DDC

Blood test	*n*	Mean	Median	Standard deviation	*P* value
Hb P1	34	13.35	13.2	0.98	
Hb P2	34	11.57	11.45	1.25	
Hb P3	33	11.62	11.7	0.93	<0.001
ESR P1	26	19.38	14.5	13.44	
ESR P2	29	42.21	41	18.76	
ESR P3	23	33.57	29	17.64	<0.001
CRP P1	29	0.25	0.2	0.21	
CRP P2	30	0.91	0.33	1.33	
CRP P3	24	1.55	0.24	6.28	0.024

DDC, dose-dense chemotherapy; Hb, hemoglobin (g/dl); P1, measurements before AC protocol; P2, measurements after AC protocol; P3, measurements at the end of paclitaxel treatment; ESR, erythrocyte sedimentation rate (mm/hr); CRP, C-reactive protein (mg/dl).

Table 4. Vital signs during DDC

Measurement	*n*	Mean	Median	Standard deviation	*P* value
SaO2 P1	30	98.87	100	1.41	
SaO2 P2	28	99.04	100	1.37	
SaO2 P3	28	99.13	99	0.86	0.996
Systolic P1	30	137	131	29.86	
Systolic P2	31	130	132	19.32	
Systolic P3	27	135	135	24.41	0.007
Diastolic P1	30	80.43	80	14.37	
Diastolic P2	30	77.87	75	10.40	
Diastolic P3	27	81.04	80	12.56	0.061
Pulse P1	31	81	80	12.61	
Pulse P2	29	84	86	12.11	
Pulse P3	27	86	83	11.64	0.472

SaO2, saturation in %; blood pressure in mm/Hg; pulse in beat/minute. DDC, dose density chemotherapy; P1, measurements before AC protocol; P2, measurements after AC protocol; P3, measurements at the end of paclitaxel treatment.

possibly argue that part of the documented fatigue is actually expression of mild dyspnea, and the true incidence of this phenomenon may be underestimated in previous studies. A review of DDC from MSKCC reported on 162 patients concentrating on the dosing and drug delivery and on classic grades 3 and 4 toxicity [19]. As this retrospective study did not assess pulmonary function and as in our study the complaints of dyspnea were mild, it is not surprising that they did not uncover pulmonary toxicity. They did have one case of grade 5 pneumonitis which occurred after the subject's first cycle of paclitaxel.

Growth factor support is considered mandatory for proper and safe delivery of the dose-dense schedule of chemotherapy and for many other adjuvant regimens. Recent data suggest, however, that it may be necessary only during the duration of doxorubicin and cyclophosphamide in the DDC protocol and

not required for biweekly paclitaxel [20]. In our study, the major decline in function, however, was during the initial 8 weeks when cytokine support is mandatory. CRP level and ESR, both acute phase reactants, increased during treatment in the present study. These changes may be an expression of an inflammatory process taking place in the lung parenchyma causing a reduction in the perfusion. Whether this inflammatory process is a result of the growth factors or the chemotherapy cannot be ascertained in the present study. Given that all our patients received i.v. long-acting steroids in the first 8 weeks of paclitaxel therapy and that their lung injury remained after completion of the paclitaxel, we assume the steroid regimen used in the trial had no preventive effect on the lung toxicity.

Children treated for lymphoma with chemotherapy with and without radiation were found to have a significant reduction in pulmonary function tests at a median follow-up of 5 years. Interestingly, however, none of these patients reported any respiratory symptoms [21]. After 5 years, abnormal pulmonary function tests persisted in 13% of the pediatric population. A concern with our findings in the breast cancer population is that many women receiving dose-dense therapy will also be exposed to breast radiotherapy that involves some of the lung parenchyma and can potentially cause long-term lung injury. To determine the duration and reversibility of our finding, we are performing follow-up studies of the patient population at 6 and 12 months with potential long-term assessments.

In conclusion, patients with breast cancer, adjuvant DDC appear to significantly reduce pulmonary function. This may be attributed to the combination of the doxorubicin–cyclophosphamide regimen with G-CSF support as the greatest changes occurred during this part of therapy. Longer and larger follow-up studies are needed to confirm our findings and to determine the underlying mechanism of this observation. Awareness of this newly described toxicity could be important in women with preexisting lung disease and when choosing the optimal adjuvant chemotherapy regimen. In the past, we have concentrated on the acute and obvious side-effects of our therapies. As the outcomes of women with breast cancer improve, our goal should be to further decrease the more subtle and possibly long-term toxic effects while continuing to improve survival.

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