Dose-Dense Nonpegylated Liposomal Doxorubicin and Docetaxel Combination in Breast Cancer: Dose-Finding Study

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ABSTRACT

Background. Anthracyclines and taxanes are effective drugs in breast cancer (BC), but their toxicity profiles limit their use in combination. A dose-finding study was performed to determine maximum tolerated doses (MTDs) of nonpegylated liposomal doxorubicin (TLC-D99) and docetaxel (DTX) as a dose-dense schedule, to maintain dose intensity, and to limit toxicity, particularly cardiac.

Methods. Twenty-four patients were enrolled, 12 with metastatic BC, 5 with locally advanced BC, and 7 with early BC. An intra- and interpatient approach was planned in two sequential steps. In the first step, TLC-D99 was administered at dose levels of 40, 45, and 50 mg/m² plus DTX at a fixed dose of 50 mg/m². In the second step, TLC-D99 was administered at the dose established in the first step plus DTX at dose levels of 55, 60, and 65 mg/m². Every treatment cycle was delivered on day 1 every 14 days. Pegylated granulocyte colony-stimulating factor was scheduled on day 2. Dose-limiting toxicities (DLTs) were defined as G4 hematological; G3 nonhematological; $\geq 10\%$ or $\geq 20\%$ left ventricular ejection fraction (LVEF) reduction if the final value was $< 50\%$ or $\geq 50\%$, respectively; severe arrhythmia; and symptomatic heart failure. LVEF was evaluated by echocardiography every two cycles, and precursor brain natriuretic peptide (pBNP) and cardiac troponin I (cTnI) were monitored on days 1 and 2.

Results. Five DLTs occurred (20.8%). No cardiac event of congestive heart failure was reported; 2 events of grade 3 cardiac dysfunction (8.3%), including a $\geq 20\%$ LVEF reduction in 1 patient and symptomatic arrhythmia in another; 2 incidences of G4 neutropenia (8.3%); and 1 occurrence of G3 asthenia (4.2%) were reported. MTDs were not reached. The recommended doses were established as TLC-D99 50 mg/m² and DTX 65 mg/m². Cumulatively, mild (G1–G2) cardiac dysfunction was observed in 58.4% of patients: G1 cardiac

arrhythmia was noted in 50%, G1–G2 general cardiac toxicity occurred in 25%, and concomitant toxicity was present in 17%. cTnI never increased. pBNP was increased in 25% and was associated with limiting arrhythmia in 4% and cardiac dysfunction in 16%.

Conclusion. Dose-dense TLC-D99 50 mg/m² and DTX 65 mg/m² can be safely administered in combination every 2 weeks for breast cancer, with the highest projected dose intensity for each drug at 25 and 32.5 mg/m² per week, respectively.

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DISCUSSION

The administration of an anthracycline with a taxane to patients with breast cancer (BC) has been proposed in either concomitant or sequential regimens, with the latter showing similar antitumor efficacy, higher relative dose intensities (DIs), and a reduced incidence of febrile neutropenia [2]. The major challenge with their concomitant use is maintaining an adequate balance between DI and toxicity.

We report our experience using nonpegylated liposomal doxorubicin (TLC-D99) in combination with docetaxel (DTX) in a dose-dense schedule using liposomal doxorubicin to limit cardiac toxicity. Based on our experience, doses of 50 and 65 mg/m² for TLC-D99 and DTX, respectively, administered every 2 weeks are recommended as first-line or primary chemotherapy for breast cancer patients.

Dose-limiting toxicities were observed in 5 of 24 patients (20.8%), including G3 cardiac dysfunctions in 2 patients (8.3%), G4 neutropenia in 2 patients (8.3%), and G3 asthenia in 1 patient (4.2%). Careful instrumental and biological monitoring of cardiac toxicity allowed us to detect cardiac dysfunctions in 16 patients (66.7%), with mild cardiac dysfunction (G1–G2 not

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Table 1. Cardiac toxicity for patients and cycles

Toxicity	Patients (<i>n</i> = 24), <i>n</i> (%)				Cycles (no. = 144), no. (%)			
	1	2	3	4	1	2	3	4
Cardiac arrhythmia								
Conduction abnormality	4 (16)	—	—	—	5 (3)	—	—	—
Prolonged QTc interval	—	—	—	—	—	—	—	—
Supraventricular/nodal	10 (42)	—	1 (4)	—	15 (10)	—	1 (0.7)	—
Ventricular	—	—	—	—	—	—	—	—
Total	14 (58)	—	1 (4)	—	20 (13)	—	1 (0.7)	—
Cardiac general								
Hypertension	2 (8)	1 ^a (4)	—	—	8 (6)	1 ^a (0.7)	—	—
Pulmonary hypertension	1 (4)	—	—	—	2 (1.4)	—	—	—
Valvular heart disease	1 (4)	—	—	—	1 (0.7)	—	—	—
Diastolic LV dysfunction	3 (13)	—	—	—	12 (8)	—	—	—
Systolic LV dysfunction	—	—	1 (4)	—	—	—	1 (0.7)	—
Total	7 (29)	1 ^a (4)	1 (4)	—	23 (16)	1 ^a (0.7)	1 (0.7)	—

Abbreviation: LV, left ventricle

requiring treatment delay or dose reduction) in 14 patients (58.4%) (Table 1). The mean left ventricular ejection fraction baseline value was 67%, and this was maintained with a mean value of 66% at the completion of chemotherapy.

A previous report on first-line treatment for metastatic BC (MBC) by Alba et al. showed that significantly fewer patients completed the planned six treatment cycles with the concomitant versus sequential doxorubicin and DTX regimen (67% vs. 81%, $p = .04$) [2]. The doses administered with the dose-dense TLC-D99 and DTX schedule (50 and 65 mg/m² on an every-2-week schedule) correspond to projected DIs reported previously with sequential regimens. The dose-dense TLC-D99 and DTX schedule has been proposed at 60 mg/m² for each drug in early BC in the trial by Alvarez et al. [5].

Our study reports the highest levels of dose intensity of doxorubicin-docetaxel combination while maintaining cardiac toxicity at comparable levels to the reported anthracycline-taxane combinations [11–15].

Our dose-dense regimen of TLC-D99 (50 mg/m²) and DTX (65 mg/m²) on day 1 every 14 days reported no congestive heart failure (CHF) and 8.3% limiting cardiac dysfunctions. A previous study by Mrozek et al. reported that TLC-D99 (50 mg/m²) on day 1 and DTX (25 mg/m²) on days 1 and 8 every 21 days

failed to improve cardiac safety in first-line treatment for MBC [9]: a 10% rate of CHF (2 patients) and 1 case of asymptomatic 27% LVEF reduction in patients pretreated with adjuvant doxorubicin were reported. Schmid et al. proposed TLC-D99 (60 mg/m²) and DTX (75 mg/m²) every 3 weeks in metastatic breast cancer: no CHF and no limiting cardiac dysfunction were observed [10]. Curtit et al. reported 15% CHF (5 patients) in anthracycline-pretreated patients with the same schedule [11]. Using a weekly schedule of 3 of 4 weeks with TLC-D99 (25 mg/m²) and taxane (paclitaxel 50 mg/m² or docetaxel 30 mg/m²), Rosati et al. did not report either CHF or limiting cardiac dysfunction; the objective response rate (ORR) was 79% in association with DTX [12]. Noncardiac dose-limiting toxicities reported with our biweekly schedule were febrile neutropenia and asthenia; anemia, mucositis, and neuropathy were also reported with triweekly and weekly schedules.

Our dose-dense regimen resulted in an ORR of 67%, 59% in MBC or locally advanced BC, comparable to the every-3-week schedule (ORR of 50% reported by Schmid et al. [10] and 79% reported by Curtit et al. [11]) and the weekly schedule of Rosati et al. (ORR of 79% with DTX) [12].

Author disclosures and references available online.