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AERO-B03: A Randomized Phase II Trial of Dose-Dense Docetaxel in Node-Positive Breast Cancer

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BACKGROUND: Dose-dense, every-2-week taxane administration is one of the most promising chemotherapy regimens in node-positive breast cancer. The randomized, phase II AERO-B03 trial is assessing the feasibility of docetaxel dose-dense regimens in this setting. **METHODS:** From December 2003 to September 2004, 100 patients with node-positive breast cancer were randomized to receive six cycles of 75 mg/m² of docetaxel intravenously (IV), 75 mg/m² of epirubicin IV, and 500 mg/m² of cyclophosphamide IV every 3 weeks (TEC) (control group); four cycles of 100 mg/m² of epirubicin IV and 600 mg/m² of cyclophosphamide IV every 2 weeks (EC) followed by four cycles of 100 mg/m² of docetaxel IV every 2 weeks (dose-dense A) or four cycles of 100 mg/m² of docetaxel IV followed by four cycles of EC (dose-dense B). Patients received pegfilgrastim on day 2 of each cycle. The primary endpoint was grade 4 toxicity; if half of patients in any of the arms experienced grade 4 effects, patients in that arm would be rejected from further study. An independent safety monitoring committee reviewed the data. **RESULTS:** Patient characteristics were well balanced between the three arms (median age, 54 years [31–75 years]; pT1 = 50%, pT2 = 46%, pT3 = 4%; pN1 = 78%, pN2 = 17%, pN3 = 5%; conservative surgery, 67%). There were no toxic deaths. One patient using the dose-dense A regimen refused chemotherapy and was excluded from the analysis. One patient in each arm discontinued therapy for personal reasons; one patient in the control arm, four in the dose-dense A arm, and two in the dose-dense B arm discontinued therapy because of toxicity. In the control, dose-dense A, and dose-dense B groups, the mean dose intensities (mg/m²/w), respectively, were 24, 43, and 45 for docetaxel; 24, 46, and 46 for epirubicin; and 162, 277, and 277 for cyclophosphamide. Toxicities related to therapy appear in the table. **CONCLUSION:** Toxicity of docetaxel dose-dense arms was consistent with initial expectations. These results do not support the use of docetaxel dose-dense regimens outside the clinical trial setting. However, both dose-dense regimens seem to be good candidates for comparison with standard chemotherapy in high-risk breast cancer patients. This trial was supported by Sanofi-Aventis and Amgen.

ADVERSE EFFECT	CONTROL	DOSE-DENSE A	DOSE-DENSE B
Febrile neutropenia (infrequent)	14%	10%	3%
Grade 3–4 toxicity	43%	73%	68%
Neutropenia	29%	47%	27%
Cutaneous toxicity	0%	17%	21%
Hand-foot syndrome	0%	20%	21%
Neurotoxicity	0%	13%	9%
Nausea	6%	17%	3%
Vomiting	9%	10%	6%
Grade 4 toxicity	26%	40%	18%

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Q&A

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At what point might the use of dose-dense docetaxel treatments be considered in the clinical setting?

Dose-dense docetaxel should be considered experimental treatment for the time being and should not be used in the clinical setting as long as we do not have completed trials addressing the efficacy/toxicity balance of such treatment.

— Pascal Piedbois, MD, PhD

P E E R V I E W P O I N T

The success of dose-dense chemotherapy in CALGB 9741, using doxorubicin/cyclophosphamide followed by paclitaxel every 2 weeks with granulocyte colony-stimulating factor support, has led to other trials of dose-dense taxane-based therapy. The AERO-B03 trial, reported by Piedbois et al, was a randomized phase II study comparing TEC given every 3 weeks, with dose-dense EC followed by docetaxel or docetaxel followed by EC, with these latter regimens using every-2-week treatment cycles. Because of widespread use of filgrastim or pegfilgrastim in the dose-dense treatment arms, these arms had lower rates of febrile neutropenia. However, the dose-dense docetaxel regimens had considerably more nonhematological toxicity, including grade 3 hand-foot syndrome (21% vs 0% for TEC), grade 3 neurotoxicity (9% vs 0% for TEC), and grade 3 cutaneous toxicity (17–21% vs 0% for TEC). The authors concluded that these every-2-week, dose-dense regimens merit further study. However, the troubling rate of clinically significant nonhematologic toxicity—not mitigated with G-CSF—raises substantial concerns about the feasibility of every-2-week docetaxel.

— Harold J. Burstein, MD, PhD