New Sequential Dosing Regimen Shows Promise in Node-Positive Breast Cancer

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Sequential dosing may improve the effectiveness of adjuvant chemotherapy regimens in node-positive breast cancer, by limiting overlapping toxicity while maximizing dose-intensity, Clifford A. Hudis, MD, said at the Chemotherapy Foundation's 13th annual symposium. At Memorial Sloan-Kettering Cancer Center, where Dr. Hudis is assistant attending physician in the Breast Cancer Medicine Service, researchers are testing a sequential dosing regimen that combines doxorubicin, paclitaxel (Taxol), and cyclophosphamide, supported by granulocyte-colony stimulating factor (G-CSF, Neupogen). There is increasing evidence that higher dose intensity yields improved disease-free survival in women with four or more positive axillary nodes and that sequential dosing is superior to alternate dosing, Dr. Hudis said. He cited the Italian breast cancer study led by Dr. Gianni Bonadonna in which a sequence of four doses of doxorubicin, followed by eight doses of cyclophosphamide, methotrexate, and fluorouracil (CMF) proved more effective than one dose of doxorubicin followed by two doses of CMF in four alternating cycles. Phase II TrialForty-two women were enrolled in the phase II sequential therapy trial at Memorial Sloan-Kettering, Dr. Hudis said. All had completely resected breast cancer involving four or more ipsilateral axillary lymph nodes (median positive nodes: 8; median tumor size: 3 cm). The dosing schedule was 90 mg/m² of IV doxorubicin every 14 days × 3, followed by 250 mg/m² of paclitaxel over 24 hours every 14 days × 3, then 3 g/m² of IV cyclophosphamide every 14 days × 3. All nine cycles were supported by G-CSF on days 3 through 10. Alopecia was universal, Dr. Hudis said. Grade 3 nonhematologic toxicities included fatigue and bone pain in about one quarter of patients, stomatitis and dermatologic toxicity, neurosensory toxicity, and nausea. Fewer than 10% of patients had joint pain, diarrhea, vomiting, dyspnea, muscle aches, or edema. At the end of the trial, amenorrheic patients with positive estrogen or progesterone receptor assays (19 in all) were started on a 5-year course of tamoxifen (Nolvadex), 20 mg/day. Patients with 10 or more positive nodes, tumors exceeding 5 cm, or less than complete mastectomy (24 in all) were treated with radiation therapy. With a median follow-up of 577 days, there were 7 relapses. The disease-free survival is 85%. Dr. Hudis concluded that sequential dose-dense doxorubicin, paclitaxel, and cyclophosphamide represents a promising new regimen, with acceptable toxicity, as adjuvant therapy for breast cancer. Further studies are underway to confirm this conclusion.

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