2013 San Antonio Breast Cancer Symposium

Abstract Number: 851883

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Title: Novel targeted therapy for breast cancer chest wall recurrence: low temperature liposomal doxorubicin and mild local hyperthermia

Body: Background: Unresectable breast cancer chest wall recurrence (CWR) following radiation is very difficult to treat and often responds poorly to standard chemotherapy. Symptoms include pain, reduced range of motion, disfigurement, and skin erosions with bleeding and infection. We hypothesized that thermally enhanced drug delivery using low temperature liposomal doxorubicin (LTLD, ThermoDox®), given with mild local hyperthermia (MLHT) would be a safe and effective targeted therapy. LTLD is given by iv infusion; it then localizes in CWR tumors due to their leaky vasculature. When heated to ≥ 39.5°C, LTLD releases a high concentration of the heat-enhanced cytotoxic doxorubicin.

Methods: The results of 2 similarly-designed independent phase I trials were combined for analysis. Eligible patients had CWR progressing after radiation, hormone therapy, and chemotherapy. Subjects were to get up to 6 cycles of LTLD every 21-35 days, followed immediately by chest wall MLHT for 1 hour at 40°- 42°C. In Trial A, 18 subjects received LTLD at 20, 30, or 40 mg/m²; in Trial B, 11 subjects received LTLD at 40 or 50 mg/m². The primary endpoint of each trial was to determine the maximum tolerated dose (MTD); secondary endpoints were local objective response and the pharmacokinetic (PK) and safety profiles of LTLD. Local response was
assessed by serial photography and measurements of CWR. PK samples for total plasma doxorubicin and doxorubicinol were collected at Cycle 1 and Cycle 2 for both trials.

**Results:** Twenty-nine subjects were enrolled and received ≥ 1 cycle (median 4, range 1-6). Median age was 57; 16 (55%) had triple negative disease and 13 (45%) had distant metastases. The median prior exposure to anthracyclines was 256 mg/m^2^ and the median prior dose of radiation was 6,100 cGy. Thirteen subjects were evaluable for MTD in Trial A and 9 in Trial B. Trial B established a phase II dose of 50 mg/m^2^ recommended by a Data Safety Monitor Board, based on 1 of 6 subjects at the 50 mg/m^2^ dose level having a DLT (grade 3 hypokalaemia unrelated to study treatment). In Trial A, 2 of 7 subjects at 40 mg/m^2^ had a DLT (grade 4 neutropenia lasting > 5 days; grade 3 dehydration lasting 27 days). The C_max Concentrations between 18,400 to 20,700 ng/mL were consistent at an equal dose level (40 mg/m^2) between trials. Altogether, 7 (24%) subjects developed reversible grade 3-4 neutropenia and 4 (14%) reversible grade 3-4 leukopenia. No cardiac toxicity or hand-foot syndrome was seen. One case of CW thermal burn (grade 3) and one case of radiation recall (grade 2) were reported. Five (17%) complete local responses and 9 (31%) partial local responses were seen. The rate of local response was 48% (14/29; 95% CI: 30%-66%). Seven of 29 subjects (24%) progressed outside the study treatment field.

**Conclusion:** LTLD plus MLHT is a novel therapy that is safe and produces objective responses in heavily pretreated CWR patients with limited therapeutic options. The primary toxicity is reversible bone marrow suppression. A phase II trial is ongoing at the MTD (50 mg/m^2). Future work should test thermally enhanced LTLD delivery in a less advanced, less heavily pretreated patient population.

*Author note-Dr. Dewhirst and Dr. Blackwell equally contributed

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