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Meeting abstract

Local drug delivery to the breast: a phase I study of breast cytotoxic agent administration prior to mastectomy

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Background

Intraductal administration of cytotoxic agents has been shown to inhibit the development of breast cancer in Her-2/neu over-expressing mouse and MNU rat models. This dose escalation study was performed to demonstrate the safety of this approach in women prior to mastectomy.

Methods

The study was performed in Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China where the standard of care includes a long preoperative hospital stay prior to mastectomy. Two drugs, pegylated liposomal doxorubicin (PLD) and carboplatin (C) were administered at 3 dose levels (PLD: 10,20,50 mg and carboplatin 60,120,300 mg) with the highest dose approximating the clinical intravenous dose. There were five subjects in each group with 15 subjects treated with each drug. Study drug was administered once per subject. Upon obtaining informed consent, subjects underwent a local nipple block and cannulation of 5–8 ducts with intraductal instillation of the drug. Venous blood samples were obtained for pharmacokinetic analysis. The total dosage was divided by the number of cannulated ducts to yield a dose per duct. The breast was removed surgically as planned 2–5 days post treatment and the treated ducts were marked to enable identification on pathological evaluation.

Results

Intraductal administration was generally well-tolerated with mild, transient breast discomfort upon administration associated with the rate of infusion. Clinically significant laboratory adverse events were limited to decreases in hemoglobin following mastectomy, consistent with blood loss. Neither leucopenia nor thrombocytopenia were observed in the study. In the carboplatin arm, three women at the 300 mg dose experienced mild nausea and vomiting. In the PLD arm most women had mild erythema and swelling of the breast over the 72 hours following the drug administration while the women receiving the highest dose experienced local erythema until the time of surgery.

Pharmacokinetic analysis showed that carboplatin rapidly entered systemic circulation with an early peak time (tmax~30 min) with a resultant PUF AUC (area under the curve) consistent with the Calvert Formula using estimated GFR. Total plasma doxorubicin had delayed peak concentration times (tmax >36 hours) with a linear dose response and peak concentrations substantially lower than expected from equivalent IV dosing. No doxorubicinol metabolite was detected in the plasma.

Pathological examination showed the drugs were widely distributed throughout the ductal systems reaching terminal duct lobular units, and there was a significant although variable dose-related epithelial cell loss in ducts with dye indicating drug effect. While dye was seen in or

near the cancer areas, the effect of drug treatment on the disease could not be distinguished.

Conclusion

This study demonstrates that cytotoxic drugs can be easily administered into breast ducts with minimal toxicity.

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