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Meeting abstract

Intraductal pegylated liposomal doxirubicin may achieve long term protection in HER2/NEU transgenic mice by restricting mammary gland outgrowth

S Sukumar*, T Mori, YS Chun, C Zahnow and D Huso

Address: Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Email: S Sukumar* - saras@jhmi.edu

* Corresponding author

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This work is based on the hypothesis that intraductal injection can treat existing lesions and prevent future breast cancers originating in the epithelial cells lining the breast ducts. We have previously demonstrated our ability to access the entire mammary gland through the teat in mouse and rat mammary tumor models. Further, we showed that several other common chemotherapeutic drugs such as 5 fluorouracil, carboplatin, and methotrexate were effective, but not to the same extent as PLD. Thus, intraductal injection of PLD has potential in the prevention and neo-adjuvant therapy of breast cancer.

Recently, we observed that in addition to rendering the mammary glands tumor free for more than 3 months after all of the control animals had developed multiple tumors, mammary glands of PLD treated mice were stunted in their growth. Instead of the florid growth with multiple branches and side branches studded with terminal end buds, akin to a "spring tree" seen in normal glands the PLD treated mammary gland presented the aspect of an "autumn tree". In the transgenic mice, the epithelial cells in the entire mammary gland express the MMTV-Her2/neu transgene and at even higher levels during pregnancy. This raised the concern that stimulation of proliferation of these cells, for example, by pregnancy, may result in a higher incidence of spontaneous mammary tumors in the PLD treated mice.

What then is the response of this treated mammary gland to a new pregnancy? To test this concept, we induced pregnancy in PLD treated mice. Her2/neu mice treated with intraductal PLD, like their untreated controls, had normal deliveries, with pups of normal weight and number in the litter. However, unlike control mice, their pups survived for less than one week. Long term follow-up showed that pregnancy did not increase the incidence of tumors in PLD treated mice. Their mammary glands showed a very poor proliferative response to the pregnancy hormones and remained stunted in their growth. It is likely that PLD not only affected the eradication of preneoplasias but also resulted in a depletion of normal mammary gland stem cells This concept is being tested by determining the difference in stem cell content between untreated and PLD treated glands by transplantation of serial dilutions of epithelial cells from sham and PLD treated glands into cleared mouse fat pads, examination of markers of stem cells, such as ALDHA, etc. If proven to be the case, these findings raise the possibility that long term protection may be achieved by intraductal injection of PLD to women at high risk of developing breast cancer.