WILL SOM230 BE EFFECTIVE IN TREATING DUCTAL CARCINOMA IN SITU? A PROOF OF PRINCIPLE TRIAL

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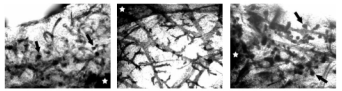
BACKGROUND

232,620 new cases of breast cancer are expected in the U.S. in 2011 (39,970 of these will die). Blockade of estrogen action can prevent breast cancer in up to 50% of women with atypical hyperplasia, and reduce invasive breast cancer in patients with ductal carcinoma in situ (DCIS) after surgery and radiotherapy. More effective treatments might improve outcomes and have more far reaching effects.

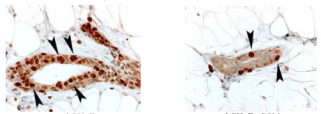
BIOLOGICAL BACKGROUND: We have found that blocking the action of IGF-I, not only blocks the action of estrogen, but also that of progesterone (1). Theoretically, blockade of IGF-I action might also inhibit actions of IGF-I that are independent of estrogen and progesterone. These might include IGF-I induced proliferation of breast cells in the absence of estrogen and effects of IGF-I on stability of genes (2).

PHARMACOLOGIC BACKGROUND: For treatment, we have chosen a multiligand somatostatin analog, called SOM230 (pasireotide), that inhibits IGF-I action by 1) reducing growth hormone secretion from the pituitary gland, and 2) by directly inhibiting IGF-I action in the mammary gland (3). The figure below shows representative whole mounts of mammary gland from hypophysectomized, oophorectomized rats treated with bGH (left), bGH + SOM (middle), and bGH + SOM + excess IGF-I (right). SOM230 prevented bGH-induced formation of terminal end buds in the mammary gland (4), but the inhibition by SOM230 was overridden by additional IGF-I.



bGH+E_2 bGH+E_2+SOM bGH+ E_2+IGF-I+SOM

The figure below shows cell proliferation (Ki67) in a mammary gland from a hypophysectomized, oophorectomized rat treated with bGH + E_2 (left). The right figure is from a similarly treated animals with the addition of SOM230. Note the remarkable reduction in cell proliferation



SOM230 VS. TAMOXIFEN:

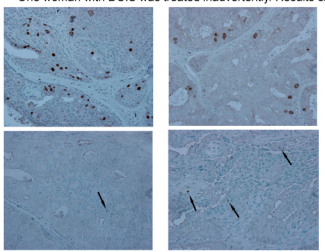
Although we did not do a direct comparison of the effectiveness of SOM230 vs. tamoxifen, we tested the effects of very high doses of both medications on their ability to prevent or reverse hGH and E_2-induced mammary hyperplasia in female rats (hypophysectomized and oophorectomized at 21 days of age). We found that although tamoxifen did not appear to be as effective as SOM230, the fact that it did not enhance the action of SOM230 indicates that SOM230 is at least as effective as tamoxifen (5).

TRANSLATION TO HUMANS

We were awarded a DoD Synergistic Idea award (2006) entitled "Breast Cancer Chemoprevention by SOM230, an IGF-I Action Inhibitor: a proof of principal trial". It was designed to determine whether inhibition of IGF-I action by the somatostatin analog, SOM230, would inhibit cell proliferation and stimulate apoptosis in typical or atypical hyperplastic lesions in women, as it did in rats.

FINDINGS

- We have not yet published our findings. Therefore, we are limited in how much we can report.
- We treated 13 women carrying a diagnosis of atypical hyperplasia of the breast with SOM230 for 10 days. SOM230 significantly inhibited cell proliferation and increased apoptosis , as it had in rats.
- One woman with DCIS was treated inadvertently. Results can be seen below.



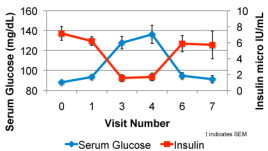
Photomicrographs through sections of DCIS before (left) and after (right) treatment. Cell proliferation was reduced from 3.4% to 0.9%.

There was a small increase from 0.1 to 0.4% in apoptosis, as demonstrated in the two lower photomicrographs.

SIDE EFFECTS:

Side effects included moderate hyperglycemia due to inhibition of serum insulin. This graph shows the relationship of glucose to insulin before, during and after stopping SOM230. There was also a reduction in serum IGF-I (still mostly within the normal range), which also returned to baseline after stopping SOM230.

Mean Fasting Serum Glucose and Insulin Levels



BC097854 - "WILL SOM230 BE EFFECTIVE IN TREATING DUCTAL CARCINOMA IN SITU? A PROOF-OF-PRINCIPLE CLINICAL TRIAL"

We hypothesize that blockade of IGF-I action by SOM230 will, in principle, be effective in treating ductal carcinoma in situ (DCIS), by inhibiting cell proliferation and angiogenesis, and increasing apoptosis in tumors.

SPECIFIC AIM 1: To determine whether SOM230 will inhibit cell proliferation and angiogenesis, and stimulate apoptosis in tissue samples from excision biopsies in comparison to core biopsies from women with ER positive DCIS. Also to assess the effects of SOM230 on phosphorylated IGF-IR and IRS-1.

SPECIFIC AIM 2: To determine whether treatment with SOM230 for 19.5 days will inhibit tumor volume, morphologic and kinetic features by mammography and dynamic contrast enhanced MRI (DCE-MRI).

SPECIFIC AIM 3: To determine whether the early effects of SOM230 on serum insulin and glucose will abate by 20 days of treatment.

PROTOCOL: We will enroll 24 women with DCIS, with stratification by tumor grade (low, intermediate, high). Each of these grades will be assessable by including 8 patients in each group. This will also permit evaluation of the group as a whole. In addition to histological endpoints, we plan to correlate the tissue results with physiological and tumor volume endpoints by DCE-MRI (Aim 2), and also mammography. This increase in time of exposure to SOM230 will also permit evaluation of whether during continued use of this drug, glucose abnormalities will resolve, as they have in previous studies on other disorders (Aim 3).

DCE-MRI

•We are in the process of developing a pharmo-kinetic model to assess vascular permeability of premalignant and invasive breast cancer by MRI.
•When tumors develop there is increased blood flow and increased permeability. Our model will permit measuring blood flow relative to the aorta vs. tumor.
•Thus DCE-MRI will allow us to assess tumor volume and behavior.

CURRENT PROGRESS: During the last 7 months we obtained approvals from the New York University School of Medicine IRB, CTSI, NYU Cancer Center PRMC, Bellevue Hospital and New York Harbor Health Care IRB. In addition we were approved to start enrollment in June 2011 by the DoD and FDA.

We hired a Research Coordinator and a Research Scientist. We have developed the data entry program and CRFs and set up new protocols for immunostaining and Western blotting.

BC103983 - "EFFECT OF PASIREOTIDE IN BREAST CANCER PREVENTION IN BRCA1 DEFICIENCY"

A basic science expansion grant has been recommended for funding by the DoD. We have recently discovered a novel model of Brca1 deficiency with an extreme phenotype consisting of highly dilated ducts and premalignant hyperplastic lesions. We now wish to employ this model to determine whether pasireotide is effective in treating development of the phenotype and tumor formation.

BRCA1 plays a central role in DNA damage responses, regulating centrosome duplication and genomic instability. Moreover, several high-profile publications have shown that BRCA1 loss or mutation affects the mammary epithelial hierarchy, which in turn affects the rate and type of cancer that develops. Our studies will determine whether IGF-I blockade not only reverses gross morphological phenotype via inhibition of proliferation but also restores genomic stability and normal distribution of mammary cell lineages. These studies are critical for assessing the idea that breast cancer prevention in BRCA1 mutation patients can be achieved by blocking a key role of IGF-I.

SUMMARY

1. We have found that IGF-I is essential for mammary development and underlies the actions of estrogen and progesterone.
2. Inhibition of IGF-I by various means, including a multiligand somatostatin analog, SOM230 (pasireotide), prevents mammary development and hyperplasia by inhibiting cell proliferation and stimulating apoptosis.
3. In a proof of principle trial in 13 women with atypical hyperplasia, we found that short-term administration of SOM230 significantly inhibited cell proliferation and increased apoptosis.
4. The medication was generally well tolerated but had a side effect of moderate hyperglycemia due to insulin inhibition.
5. We are now actively recruiting volunteers with DCIS for our present clinical expansion grant.
6. We have developed a novel mouse model of *Brca1*$^{(-/-)}$ deficiency to determine whether inhibition of IGF-I action will prevent the phenotype and tumor development. Also to be tested is whether IGF-I blockade will inhibit centrosome duplication and genomic instability.

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