

Hot Topics Scholarship Advocate Reports from the 2007 San Antonio Breast Cancer Symposium

Topic: HER2-related treatment approaches

Report Name	Pages	Author
Molecular Imaging for Breast Cancer Diagnosis	2-7	Amy Bonoff
Vaccines for Her2 Breast Cancer	8-9	Liz Frank
The Safety and Efficacy of Trastuzumab following Adjuvant Chemotherapy in Node Positive HER2-Positive Breast Cancer	10-12	Claudine James
Neoadjuvant Treatment of Lapatinib for Breast Cancer Stem Cells	13-14	Ann Henrick

Molecular Imaging for Breast Cancer Diagnosis

Molecular Imaging encompasses many different techniques. The various non invasive imaging methods include computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI). The research goal is to find improved non invasive diagnostic tools for detection and treatment evaluation of invasive breast cancer tumors. This paper will address an emerging technology, Diffuse Optical Spectroscopy (referred to as DOS) and briefly discuss another, more mature, technology PET, in contrast.

Explanation of Diffuse Optical Spectroscopy technology

Optical imaging studies how tissue interacts with light. DOS, in simple terms, measures how much light a tissue absorbs. DOS uses near infrared light with a range of colors, or spectra, mostly undetectable to the naked eye. Tissues have unique color characteristics according to their component parts. DOS is able to decompose that unique tissue by recognizing the colors of those component parts and so figure out the makeup of that tissue. The four key components, or biomarkers, are lipids, water, oxygenated hemoglobin (oxyhemoglobin) and deoxygenated hemoglobin (deoxyhemoglobin). Each bears a distinct spectral shape, or fingerprint, as plotted on a graph using absorption and scattering on the vertical axis and wavelength on the horizontal axis.

The concentration levels of these markers have been shown to differentiate malignant lesions from normal breast tissue. If this is true, we should be able to use this technology to detect invasive ductal carcinomas and to see how tumors respond to chemotherapy treatment. In the following discussion, it should be noted that DOS is a relatively new and unproved technology. This paper will detail some of the studies attempting to prove that DOS can both detect tumor and evaluate response. However, the studies are still preliminary, with a very small patient population, and have yet to be verified with proper clinical trials. Hopefully this technology will be able to impart information that is not currently available using the more mature molecular imaging approaches.

Detection and Monitoring

DOS studies have been able to quantify subtle changes in biological composition in thick tissue, allowing for heightened differentiation of the cells, the vasculature and the intracellular matrix. The DOS biomarkers unearth key physiological information. The total hemoglobin concentration sheds light on vascularity and angiogenesis; tissue oxygen saturation reflects tissue metabolism; lipid concentration indicates breast density or fat thickness under the skin; water content is a marker for inflammation, edema. Tumors display higher levels of water, deoxy-hemoglobin and oxy-hemoglobin and decreases in lipids in contrast to normal tissue

These differences in levels of concentration of the biomarkers between the diseased breast and normal tissue are greatest in the youngest set of patients. Those less than 30 years of age show the greatest scale of difference in shape and amplitude of the spectra, when observing the graphs of biomarker patterns. In women over 50 years of age, the markers do not show the same degree of differentiation. DOS is not currently a diagnostic tool, but the hope is that DOS imaging will be able to act as a complement to mammography for the dense breasts of younger women where mammography has been shown to be less effective than in the women over 50 years of age.

In one study, working with 12 patients between 30 and 39 years of age, with locally advanced stage 3 invasive disease, the DOS biomarkers showed statistically significant differences between the tumor and the normal tissue in the contralateral breast of each patient. Total hemoglobin, oxyhemoglobin and oxygen were almost two times the level of normal tissue and the lipids measured almost 50% less.

In another example of an admittedly still preliminary body of work, DOS biomarkers were measured before and again at the end of the first week of chemotherapy for a patient in a neoadjuvant setting. The markers showed changes in the tumor tissue, prior to any anatomic changes which would be captured in conventional imaging and palpation. After only one day of treatment, several biomarkers had notable changes. Total hemoglobin decreased by 30% where the lipids showed a 20% increase. A contrast measure, the Tissue Optical Index (the simple formula for TOI is water multiplied by deoxyhemoglobin divided by lipids), decreased 60% at the end of the first week of treatment. The marked changes in the diseased breast tissue of this

young patient seem to be an early indicator of cell death, through the decrease in the hemoglobin markers, indicating reduced oxygen consumption and loss of cellular water, or edema. If this can be clinically proved in large studies, it could change the standard evaluation of response, which is to track the changes in size of a tumor over months. Studies have already questioned decreases in size of a tumor as an adequate predictor of response.

Use of DOS To Predict Chemotherapy Response in Locally Advanced Breast Cancer

One of the most difficult clinical issues with locally advanced breast cancer is evaluating response to chemotherapy which turns out to be an indicator of a good long term survival prognosis. The current options available are palpation, ultrasound and mammography as well as MRI and PET scans. None are completely effective and tend to be given at infrequent intervals. The other major thrust of work in DOS is to look at the biomarkers as an indicator of chemotherapy response and final pathological outcome.

DOS technology is able to monitor chemotherapy from a predictive stage before treatment, through long term treatment with end stage prediction. In a study of 11 patients before, during and after a 3 cycle treatment of Carboplatin, Abraxane and Avastin therapy, the DOS biomarkers showed a different pattern for responders and non responders. In particular, the deoxyhemoglobin was reduced in the responders and showed little change in the non responders. Other markers showed changes, but less pronounced than the deoxyhemoglobin. By day 6, the deoxyhemoglobin showed 83% sensitivity and 100% specificity and if one combined the hemoglobin with the water marker, 100% was achieved by both measures. The simplicity of the scan allows for daily measurement and can follow the changes in the tissue, where, in one case, the tumor showed shrinkage followed by resurgence of the invasive tumor. It is important to note that early changes in the biomarkers do not necessarily correlate with final prognosis and the tumor can grow back after a strong initial response.

Using post surgery pathology to validate response in this 11 patient study, which used an antiangiogenic therapy, the MRI, usually a high predictor of response, only showed a 60% predictive outcome. DOS had 85% overall accuracy, predicting 96% of total responders, 100% of non responders and 96% of partial responders. MRI may not be as sensitive to antiangiogenic

changes since it uses a vascular contrast agent, one possible explanation of the relatively low predictive response in this study.

Positron Emission Tomography (PET) Imaging

In the final portion of the symposium, Eric Rosen discussed functional imaging and Positron Emission tomography, or PET. PET is a mature imaging technique and the discussion was directed towards defining the areas of effectiveness for the use of PET scans. PET has been shown effective for analyzing large primary breast cancers. It is not as effective for small tumor size or low histologic grade tumor such as a lobular cancer, with a substantial false negative rate. In that case, an MRI would be the better imaging instrument.

In trying to triage alternate methods of imaging, PET scanning has a high level of accuracy in identifying a small group of patients with locally advanced breast cancer where there is a high likelihood of distant metastases and axillary involvement which call for a full body scan. There seems to be a role for PET in staging for confusing situations, without a clear tumor, but cost can be an issue. PET also shows promise in predicting response to chemotherapy. One can measure uptake FDG, the contrast radioisotope, where a decrease in uptake FDG correlates to discrimination between responders and non responders even with a minimal decrease in tumor size. PET appears to be more discriminating in predicting the response of a primary and metastatic lesion in the early stages of treatment. DOS makes similar claims of effectiveness. PET scanning has an important prognostic and predictive value in large and unclear tumors, but is less sensitive to small micrometastases. The approval of new contrast agents is expected to increase the level of predictive response and is an area worthy of further studies.

Advocacy Perspective

The most far reaching patient advocate benefit of DOS technology is the simplicity and functionality of the DOS instrumentation. The laser breast scanner, a hand held probe, is lightly passed over breast tissue, a fast and painless procedure. The scanner can travel to remote regions, rather than requiring a patient to visit a major hospital center to be scanned. The NTROI, (Network for Translational Research in Optical Imaging), centers working on DOS, are looking towards even greater miniaturization. The electronic table top with board level components will become chip level components in the future, similar to the miniaturization in the digital

entertainment field, resulting in a miniature portable, non invasive, non ionizing method of imaging. The portable structure can easily be used in conjunction with an MRI or other imaging technology to produce a clearer, more sensitive readout.

On the other hand, the PET process, which produces superior sensitivity, involves probes that must be made with a cyclotron (an accelerator in which charged particles such as protons, are propelled by an alternating electric field in a constant magnetic field). These probes are short-lived so the cyclotron must be on site, limiting patient access. These factors can make the PET scan prohibitively expensive.

The Diffuse Optical Spectroscopy process does not introduce any foreign material. It can therefore be used repeatedly without adverse reaction. In contrast, PET scanning needs an external infusion of a potential irritant, the radioisotope used for contrast.

Finally, and most importantly, DOS functionality can enhance the working relationship between the physician and patient. Treatment of breast cancer is quickly evolving into an individualized treatment regimen based on the specific characteristics of the tumor tissue and not based on the “standard of care treatment” which has been the AC or Adriamycin-Cytoxan chemotherapy. If DOS clinical trials bear out the preliminary studies reported in this paper, there will be a new, dynamic interaction between physician and patient, as the physician can measure tumor response and adjust therapies in the office rather than waiting for the infrequent follow up scans that are now in use.

Conclusion

The new translational non invasive imaging is important for the detection and monitoring of invasive ductal carcinomas. It is particularly effective for dense tissues and for frequent screening in younger high risk women.

In detection, it promises a highly sensitive response prior to significant tumor anatomic changes. Complete response is a key predictor for long term survival.

DOS is portable and individualized allowing for therapeutic monitoring of multi stage chemotherapy regimen. Since there is no limit on usage, it allows frequent office or bedside use

to monitor response, calibrate drug dosage and adjust treatment on an individualized basis. It is compatible and complementary with any exogenous scanning techniques such as MRI or PET.

There is also potential to more easily evaluate the design of novel drugs and drug combinations in this individualized therapeutic treatment environment.

These are the potential uses for Diffuse Optical Spectroscopy. DOS is still primarily a lab based technique. Improvements are needed in qualitative and quantitative accuracy, both of which are limited by poor spatial resolution. PET scanning on the other hand has the sensitivity but not the versatility of use that DOS can provide. However, there are many issues still to be addressed in DOS, such as the need for a more sensitive spectroscopic tool that clearly distinguishes between a cancerous tumor and fibroadenoma, both of which can exhibit a similar pattern in the current imaging. And finally, clinical trials are needed to confirm the work discussed in this paper using a significantly larger patient population.

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Mini symposium 3

Posters #5010, 5036 and 6010 and articles on which posters were based
Recent Advances in Diffuse Optical Imaging, AP Gibson, JC Hebden and SR Arridge
Discussion with Albert E. Cerussi, Beckman Laser Institute

Vaccines for Her2 Breast Cancer

Her2 breast cancer accounts for about 25 percent of all women diagnosed with breast cancer. In Her2 positive patients, there is a genetic alteration in the Her2 gene resulting in the over production of the Her2 protein on the tumor cell surface. Women diagnosed with Her2 positive disease are likely to be treated with Herceptin (Trastuzumab), a therapy which targets the Her2 protein. Herceptin has been found to be extremely effective, but unfortunately, some patients will eventually develop resistance to Herceptin, resulting in a return of their disease.

Although the use of vaccines is a common way of building up the immune system to fight disease, it is a relatively new and experimental concept in breast cancer treatment. The study presented by Dr. Steven Limentani, reports on a vaccine designed to prompt the immune system to target a specific portion of the Her2 protein in breast cancer patients. Once the immune system becomes aware of the antigens in the vaccine, it responds by making antibodies, which are specialized fighter proteins that one's body produces. The hope is that these antibodies will attack and destroy any remaining cancer cells. T cells are one of five types of white blood cells. Measuring the amount of T-cell activity in response to the immunotherapy or vaccine is one way of measuring the effectiveness of that vaccine.

This study by Limentani et al., reported on a therapeutic cancer vaccine, in both the adjuvant and metastatic settings. It was designed to prompt the immune system to target a specific portion of the HER2 protein in breast cancer. The vaccine, dHER2 Antigen Specific Immunotherapeutic, was tested in the adjuvant setting as a Phase 1 trial involving 61 patients. It was also tested in a Phase 2 study, and included 38 patients with metastatic breast cancer. In both studies, the vaccine, dHER2 ASCI was well tolerated. Importantly, no symptoms of cardiotoxicity were recorded. Although there was some evidence of an antibody dose response in the adjuvant setting, the vaccine showed the greatest promise in the metastatic setting, where it was observed that one complete response and two stabilizations of disease were obtained from 13 patients when the vaccine was given as a first line therapy. Importantly, in the metastatic setting, the antibody response was maintained over time. The more powerful and sustained response in the

metastatic study than in the adjuvant one was surprising because scientists have long believed that the tumor burden was too great in advanced stage cancer for a vaccine to work effectively.

A different type of immunotherapy was explored in a poster session by Recchia, Candeloro, Necozone et al. In this study, 100 patients with metastatic breast cancer who had been previously treated with a taxane-anthracycline combination were given an immunotherapy composed from IL-2 and RA in addition to hormonal therapy in an effort to destroy residual cancer. The objective of the study was to improve progression free survival and overall survival by building up the immune system. The treatment was well tolerated, improved the immunological response and appeared to delay disease recurrence. This regimen looks particularly promising for patients with metastatic breast cancer as a follow up to chemotherapy. A phase 3 randomized trial is set to begin later this year for patients with melanoma.

Both of these examples of immunotherapy show the greatest promise for patients with metastatic breast cancer, offering encouraging evidence that triggering the immune system might have a powerful effect on controlling cancer growth for extended periods of time as maintenance therapy.

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Abstract #22-Lecture
dHer2 cancer immunotherapeutic clinical response in breast cancer patients is associated with an induction of functional antibodies and the generation of specific T cells.
S A Limentani, G Curigliano, M Campone et al.
Poster Session #6085
Maintenance hormonal and immunotherapy in metastatic breast cancer with a clinical benefit from anthracycline-paclitaxel based induction chemotherapy.
Recchia F, Candeloro G, Necozone S, Rea S.

The Safety of Pertuzumab plus Trastuzumab in Patients with HER2-Overexpressing Metastatic Breast Cancer

Pertuzumab, also commonly known by the trade name 2C4, is manufactured by the biotech company Genentech. Pertuzumab was formerly known as Omnitarg. Pertuzumab, like trastuzumab, is a humanized monoclonal antibody. Trastuzumab monotherapy offers clinical benefit to a subset of HER2 overexpressing metastatic breast cancers. However, the majority of breast cancers that initially respond to trastuzumab-containing regimens begin to progress again within one year. Pertuzumab is the first of its class in a line of agents called “HER dimerization inhibitors.” In contrast to trastuzumab, pertuzumab is designed to target tumors that have normal, rather than overexpressed levels of the HER2 protein. These inhibitors block the ability of the HER2 receptor to collaborate with other HER receptor family members (HER1/EGFR, HER3, and HER4). It is hypothesized that the binding of the inhibitors to the HER2 slows tumor growth and ultimately kills the cancer cells. This paper will focus on the safety results of a Phase II trial of pertuzumab plus trastuzumab in patients with HER2 overexpressing metastatic breast cancer which progressed during trastuzumab therapy. The trial which was sponsored by Roche Pharmaceuticals consisted of 42 women with HER2 positive metastatic breast cancer whose disease had progressed following previous treatment with trastuzumab and chemotherapy. Of the 42 participants, 33 had ≥ 1 tumor evaluation while on treatment. The results of the 33 participants are encouraging. Specifically, one patient had a complete response (3%); five had partial responses (15%); seventeen had stable disease (21%); and ten had progressive disease (30%).

As with any drug, pertuzumab has side effects or adverse events. The most common side effects associated with pertuzumab were diarrhea (57%), nausea and vomiting (33%), fatigue (31%), rash (28%), muscle spasms (17%), cough (14%), headache (12%), dyspnoea (12%), and nasopharyngitis (12%). More than 80% of the adverse events were low grade [grade 1 or 2]. However, one participant experienced a grade 3 or higher adverse event. It is important to note that 64.3% of the participants had received prior anthracycline.

In conclusion, the trial results suggest that combining HER2-targeting agents, pertuzumab and trastuzumab, is a more effective therapeutic strategy in breast cancer compared to treating with a single HER2 monoclonal antibody. Specifically, pertuzumab and trastuzumab synergistically inhibit the growth of breast cancer cells. The efficacy and toxicity profiles were both encouraging and promising. More importantly, the two-prong attack of pertuzumab and trastuzumab results demonstrated safety in the combination and was well tolerated in the patients with HER2-overexpressing metastatic breast cancer which progressed during trastuzumab therapy.

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Neoadjuvant Treatment of Lapatinib for Breast Cancer Stem Cells

Background: Neoadjuvant therapy is treatment given prior to surgery with the goal of reducing tumor size. In the past, chemotherapy or radiotherapy has been popular options but recently targeted therapies are also being considered. Lapatinib, also known as Tykerb, has only recently started being used as a targeted therapy that works against breast cancers that have extra HER2 genes.

Targeted cancer therapies are cancer treatments that target specific characteristics of cancer cells, such as a protein, an enzyme, or the formation of new blood vessels. Targeted therapies don't harm as many normal, healthy cells as chemotherapy. Many, but not all, targeted therapies are monoclonal antibodies that work in the same way as antibodies made by the immune system. In this way, targeted therapies are very different from more traditional types of anti-cancer therapies. Herceptin (chemical name: trastuzumab) is the best known targeted therapy for breast cancer. Herceptin and lapatinib only work against breast cancers that have extra HER2 genes and make too many HER2 protein receptors.

The relationship between normal stem cells and cancer stem cells is still unclear. We do know that tumorigenic breast cancer stem cells are self renewing and that some of these cells (CD44⁺/CD24^{-/low}) are resistant to conventional chemotherapy. This presentation by Jenny C. Chang, PhD focused on results of two studies:

1. How conventional chemotherapy affects tumorigenic breast cancer stem cells
2. How a specific inhibitor, lapatinib, may affect certain pathways in this tumorigenesis.

In a study of 35 patients with locally advanced breast cancer, after completing standard chemotherapy treatment, the proportion of tumorigenic breast cancer cells had increased from 5% to 15%. These cells showed properties of self renewal and new tumors formed. As chemotherapy failed to eliminate a tumorigenic population it left behind a residual population of cells capable of increasing new tumor formation.

So the question was raised: are we missing the right target?

Dr. Chang provided an excellent graphic in the form of a cartoon. It showed an individual trying to eliminate weeds in their lawn by using a lawn mower to cut off the top of the weed. If we don't get the root of the weed, it will just keep growing back and possibly spread over the rest of the lawn. That is the crux of the second part of this study and hypothesis, getting to the root of the tumorigenic breast cancer stem cell by treating it with lapatinib in a neoadjuvant setting.

Methods: A neoadjuvant clinical trial was performed in 30 patients with locally advanced HER2 overexpressing breast cancers. These patients had tumors of 10 centimeters (the size of a large

grapefruit). They each received lapatinib (EGFR/HER2 tyrosine kinase inhibitor) given initially as a single agent for the first 6 weeks, followed by a combination of weekly trastuzumab and 3-weekly docetaxel for 12 weeks before primary surgery.

Results: After 6 weeks of oral lapatinib, there was a 60% regression in tumor size. 82% of patients had a clinical response and 18% had stabilization of disease. Unlike with chemotherapy, lapatinib treatment decreased tumorigenic CD44⁺/CD24^{-/low} breast cancer cells from 10.6% to 4.7%, and also reduced self-renewal capacity measured by MS assays (30 to 15 MS/10,000 cells, p=0.01). Additionally in a gene expression analysis there was a 40% overlap between the two gene sets therefore informing researchers about the potential pathways of self renewal.

Conclusion: There is a small sub-set of cells with tumorigenic potential that are resistant to chemotherapy. It is the cancer cells with stem cell like properties that survive. Lapatinib used neoadjuvantly prior to surgery may affect the self renewal of these tumorigenic cells and sensitize them for subsequent chemotherapy. This has interesting implications for improving the treatment of chemotherapy resistant cell populations in order to achieve long-term eradication of cancer.

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