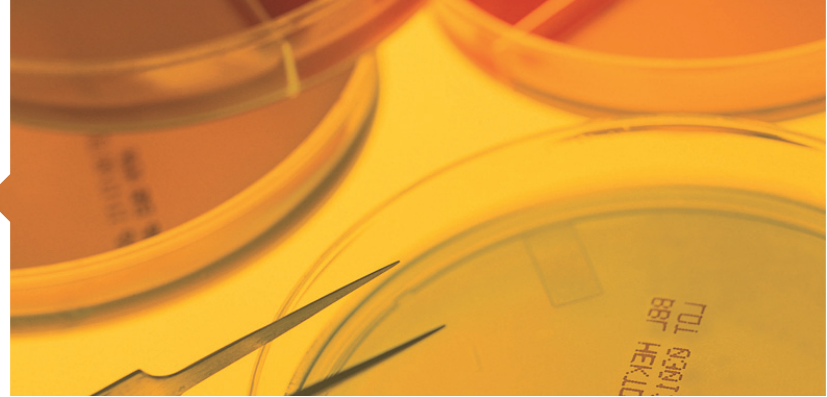


Biomarker Trends in Breast Cancer Research

Jason Hill, PhD, Associate Director,
External Science Affairs, Quintiles



Quintiles examines the novel drug combinations and mechanisms of action that will pave the way for more effective treatments.

NOVEL DRUG COMBINATIONS AND MECHANISMS OF ACTION

The biopharmaceutical industry faces continuing challenges in its mission of bringing promising new therapies to patients. These challenges are particularly acute in oncology, where the success rate of products in development is currently just 8 percent. Failures are on grounds of safety or efficacy, can be driven by the complexity of the clinical end-point and uncertainties around mechanisms of action.

Table of Contents

Novel Drug Combinations and Mechanisms of Action	01
PARP Inhibitor in Triple Negative Breast Cancer	03
Combinations of Two HER2 Targeted Drugs	04
Combinations of Anti-Angiogenic Agents and Chemotherapy	05
Conclusion	07
About the Author	07

A promising area of oncology research is the development of targeted therapies, which are drugs that target defined molecular signals or pathways. Critical to the success of targeted therapies is the use of biomarkers and diagnostics to identify the patients who are most likely to benefit from a particular therapy, allowing the right patient to be matched with the right drug. There is a need for improved tools of this kind to improve the efficiency and productivity of oncology R&D programs.

Against this backdrop, the 2009 San Antonio Breast Cancer Symposium (SABCS), held on December 9-13, included interesting new data from several new directions in research:

- > *Poly (ADP ribose) polymerase (PARP) inhibitor in triple negative breast cancer.*
- > *A combination of two HER2 targeted drugs in HER2 positive, heavily pre-treated breast cancer patients.*
- > *Combinations of anti-angiogenic agents and chemotherapy in human epidermal growth factor receptor 2 (HER2) negative breast cancer.*

PARP INHIBITOR IN TRIPLE NEGATIVE BREAST CANCER

Study results

A poster by J. Shaughnessy et al described *Final Results of a Randomized Phase II Study Demonstrating Efficacy and Safety of BSI-201, a Poly (ADP-Ribose) Polymerase (PARP) Inhibitor, in Combination with Gemcitabine/Carboplatin (G/C) in Metastatic Triple Negative Breast Cancer (TNBC)*. The study involved 116 patients, finding that the PARP inhibitor, BSI-201, improved patient outcomes. The median progression-free survival (PFS) period was 6.9 months for gemcitabine/carboplatin/BSI-201, compared with 3.3 months for gemcitabine/carboplatin alone. The median overall survival (OS) was 9.2 months for gemcitabine/carboplatin/BSI-201, compared with 5.7 months for gemcitabine/carboplatin alone.

Implications

This is a case where understanding a drug's mechanism of action and the biology of the disease has really paid off. Breast cancers that result from hereditary mutations in the genes BRCA1 or BRCA2 are known to have a deficiency in homologous recombination (HR), a major DNA repair pathway. Because of this deficiency, tumor cells are forced to use an alternate DNA repair pathway that utilizes PARP. It is also known that BRCA1- and BRCA2-deficient cancers very much resemble sporadic, non-hereditary triple-negative breast cancers. More research is needed to determine the reason for this, but it has been suggested that many sporadic breast cancers, especially triple negative breast cancers, may have alterations in, or deregulated expression of, BRCA1 or BRCA2 (or other components of the BRCA DNA repair complex).

If a cancer with a compromised DNA repair pathway due to BRCA deficiency (or an alteration that mimics BRCA deficiency) is treated with a PARP inhibitor coupled with chemotherapy – which causes DNA damage – the tumor cell no longer has an open DNA repair pathway to fall back on. Therefore, the DNA damage inflicted by chemotherapy is less likely to be repaired and the tumor cell is more likely to die. PARP inhibitors have been shown to be very effective in women with hereditary BRCA1- or BRCA2-deficient cancers, and now have shown promise in triple-negative breast cancers as well. One approach could be to determine the BRCA1 and/or BRCA2 status of

Breast cancer is the most common cancer in women worldwide, comprising 16% of all female cancers. It is estimated that 519,000 women died in 2004 due to breast cancer, and although breast cancer is thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occurs in developing countries (WHO Global Burden of Disease, 2004).

The United States has the highest annual incidence rates of breast cancer in the world; 128.6 per 100,000 in whites and 112.6 per 100,000 among African Americans (NCI SEER, 1975-2006).

the women treated in this trial, and compare it with their clinical response. It could be informative to analyze BRCA1 and BRCA2 at several levels, including expression of the proteins (such as by methods like IHC) and also direct sequencing of the genes to uncover any mutations.

COMBINATION OF TWO HER2 TARGETED DRUGS

Study results

K. L. Blackwell et al presented a poster describing an *Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy*. The study, which involved 296 women, found a statistically significant overall survival (OS) benefit in women with heavily pretreated, HER2-positive metastatic breast cancer (MBC) treated with lapatinib in combination with trastuzumab compared with those treated with lapatinib alone.

Used together, lapatinib (Tykerb) and trastuzumab (Herceptin) extended OS by almost five months in women who were failing Herceptin alone. This is an important result since this population had received on average more than six previous treatment regimens. Both products target the HER2 receptor but by different and, as this study shows, unequal mechanisms that allow lapatinib to overcome resistance to trastuzumab.

The study, which involved 296 women, found a statistically significant overall survival (OS) benefit in women with heavily pretreated, HER2-positive metastatic breast cancer (MBC) treated with lapatinib in combination with trastuzumab compared with those treated with lapatinib alone.

Implications

An important step would be to improve understanding of the mechanism of resistance to these drugs. Why does lapatinib reverse trastuzumab resistance in some women? Perhaps more importantly, is it possible to identify women who would benefit from initially receiving lapatinib instead of trastuzumab? There is a need for biomarkers in addition to HER2 to help predict which women would respond best to which drug.

The only way to answer these questions is to obtain tissue biopsies in these trials of targeted therapies. These would ideally be taken from the patient immediately prior to starting treatment, again after the patient has received the drug, and for patients who respond to the therapy, once more at the time of relapse. While the importance of obtaining tissue samples cannot be overstated, we have to be aware of the huge burden this places on the patient, and understand that our continued research can only be realized if they submit to these procedures. A consensus among Principal Investigators and treating physicians at the meeting is that we must obtain tissue from clinical studies if we are to increase our understanding of how to best match the patient with the drug. And since they are on the front line seeing the discomfort patients go through to give a biopsy, they must believe in the importance of this mission.

Although for now tissue remains the best specimen type to interrogate cancer biomarkers and signaling pathways, the “Holy Grail” of clinical cancer research is to avoid taking a painful tissue

biopsy altogether, and instead use body fluids to assess cancer biomarkers (blood, serum, etc). Circulating tumor cells (CTCs) are found in the blood of some cancer patients and could provide an alternative to a tissue biopsy. These CTCs are thought to break away from the primary (or possibly metastatic) tumor sites. Enumeration of CTCs is already in clinical use to monitor the efficacy of some treatments (a decline in the number of CTCs is an indication that treatment may be effective even if a decrease in tumor size has not yet been noted).

If CTCs are truly representative of the primary tumor, then another intriguing use of CTCs, if they can be isolated in sufficient number, is to analyze them for biomarkers or signaling pathways that you would normally look at in a tumor biopsy. Some challenges remain before CTC analysis can be deployed routinely. One is further refinement of isolation techniques to ensure that only true tumor cells are used for analysis. A second challenge is that CTCs are not found in all cancer patients, even some with heavy tumor burdens. However, the industry continues to strive towards better detection and isolation of CTCs to further aid clinicians and researchers in minimizing patient discomfort.

COMBINATIONS OF ANTI-ANGIOGENIC AGENTS AND CHEMOTHERAPY

Study results

Three posters described the impact of combinations of antiangiogenic agents – sorafenib, sunitinib, motesanib and bevacizumab (Avastin) – and chemotherapy in HER2 negative breast cancer.

A multinational, double-blind, randomized, placebo-controlled Phase IIb study of 229 patients by J. Baselga et al was titled *SOLTI-0701: A Multinational Double-Blind, Randomized Phase 2b Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo When Administered in Combination with Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer (BC)*. The study examined sorafenib – which is indicated for treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma – in combination with chemotherapy for advanced breast cancer. It found that this agent showed a trend towards improvement, but not a statistically significant benefit.

A dual-arm open-label randomized multicenter Phase II trial by H. Wildiers et al was titled *SUCON Trial (SUnitinib CONsolidation Therapy in Metastatic Breast Cancer): A Belgian Multicenter Phase II Randomized Trial in Her2 Negative Metastatic Breast Cancer Evaluating Consolidation Antiangiogenic Therapy with Sunitinib after Objective Response to Taxane Chemotherapy*. This found no evidence that sunitinib could delay tumor progression after tumor mass reduction by taxanes – in fact its performance was worse than that of the comparison therapy.

A double-blinded placebo-controlled trial of 282 patients by J. Mackey et al, titled *CIRG/TORI 010: 10-Month Analysis of a Randomized Phase II Trial of Motesanib Plus Weekly Paclitaxel as First Line Therapy in HER2-Negative Metastatic Breast Cancer (MBC)*, found that motesanib showed no benefit.

A greater understanding of the molecular biology of breast cancer has led to new post-surgical treatments, including hormone modulators and monoclonal antibodies. Many of these agents have led to decreased mortality and disease recurrence.

Survival for breast cancer between 1988 and 2000 increased by 3.6 years. The majority of these gains were due to improvements in treatment, which accounted for roughly 80% of survival gains for breast cancer alone (Sun E et al, 2008). The high rates of mortality associated with cancer magnify the value of even small absolute survival gains, since greater value is placed on a given gain in longevity, when an individual has a shorter life expectancy (Becker et al, 2007).

About 20 to 30 percent of people with breast cancer have HER2/neu-positive tumors, an aggressive type of breast cancer that was once considered highly untreatable. With the launch of the monoclonal antibody Trastuzumab (Herceptin®) in 1998, women now have multiple treatment options. Results from phase III clinical trials have shown Trastuzumab to shrink tumors and to improve survival for those with HER2/neu-positive metastatic breast cancer. Specifically, the NSABP and NCTG trials¹ and the HERA Study² demonstrated an absolute improvement in overall survival (OS) of 4.8% and 2.7% respectively.

1 Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 353(16):1673-84, 2005.

2 Smith I, Procter M, Gelber RD, et al. for the HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet.* 369(9555):29-36, 2007.

Bevacizumab (Avastin), for all of its success in other cancers such as colon cancer, showed only a modest improvement in progression-free survival (PFS) in two large trials presented at SABCS – AVADO and RIBBON 2 – but did not have a statistically significant effect on survival.

While not identical, all four of these agents have a considerable overlap in the targets they inhibit, which are primarily the receptor tyrosine kinases (RTKs) involved in angiogenesis, or the pro-angiogenic vascular endothelial growth factor (VEGF) in the case of bevacizumab.

Implications

Typically, drug development takes 10 to 15 years from inception to launch (DiMasi et al, 2003). Given this long development timeline, it would be a major step forward to understand at the earliest possible stage which cancers are most likely to respond to anti-angiogenic molecules. This would allow companies to focus limited R&D budgets on responsive cancers. Renal cell cancer has been a great success for anti-angiogenics, but as the above studies have shown, breast cancer does not appear to be as good a target for these agents.

To date, relatively little work has been done to develop biomarkers for anti-angiogenic products. Clearly though, given the differences in efficacy of these drugs in various diseases, and the sheer number of anti-angiogenics in biopharma company pipelines, more work needs to be done preclinically to identify biomarkers of response and resistance.

For compounds in development, translational research has the potential to identify likely failures at the earliest possible point, helping to optimize the returns from R&D investment.

Biomarkers or relevant signaling pathways identified in this way then need to be compared with what is known about the clinical efficacy of these drugs. There are already several completed Phase I to III studies of these agents. At a minimum, archival tissue (and even fluid if possible) should be profiled to identify potential biomarkers that correlate with response or resistance. These biomarkers could then be used to stratify patients in Phase II or Phase III trials. If one or more of these biomarkers shows a good correlation with clinical benefit, these could be used to prospectively screen patients in a Phase III trial. This would provide a true test of a biomarker's utility in selecting patients likely to respond to a given therapy.

The potential of translational science

The rapidly-advancing techniques of translational science can give biopharmaceutical companies a better understanding of the biological activity of their molecules, therapeutic targets and patient responses. This in turn helps improve clinical trial and patient outcomes.

For compounds in development, translational research has the potential to identify likely failures at the earliest possible point, helping to optimize the returns from R&D investment. For products that have already been approved for one or more indications, it offers a cost-effective way to investigate potential in other diseases and disorders. For a given molecule, translational research can improve outcomes by enabling identification of the right patient, the right combination of drugs to use, and the likely side-effects and toxicity issues.

Clinical trial biomarker support

Tissue-based testing is a critical component of the modern oncology drug development process, with key techniques including immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), tumor mutation detection and gene expression assays.

Another technology transforming biomarker research is digital pathology. This enables researchers and pathologists to look at digital images from any investigative site worldwide and eliminates issues associated with transporting and storing human tissue. By transferring these high-resolution images, researchers will no longer need to ship physical specimens, which is particularly beneficial in countries that prohibit the export of human tissue, such as China. Digital pathology increases the quality of assay standardization and harmonization, and allows more rapid testing of patient specimens regionally. This will benefit patients in clinical trials around the world by decreasing the testing time of assays that are used to match patients with the correct clinical trial.

CONCLUSION

An important trend in cancer drug development sees drugs increasingly targeting highly-selective molecular targets. Effective use of biomarkers can increase biopharmaceutical companies' understanding of how their drugs work, and also shorten the drug development process by allowing some studies to be run using surrogate marker endpoints rather than clinical measures. This approach is highly promising in helping to predict which cancers – and which patients – will respond best to which drugs. This can help bring the potential of personalized medicine to fruition in the highly challenging area of oncology.

ABOUT THE AUTHOR

Jason Hill, PhD

Associate Director, External Science Affairs, Quintiles

Jason Hill, PhD, is Associate Director for External Science Affairs at Quintiles Central Laboratories. He was formerly Director of Molecular Biology at Targeted Molecular Diagnostics (TMD), a privately held company that specialized in the development and deployment of tissue based biomarker assays for oncology clinical trials, which was acquired by Quintiles in 2008. Dr. Hill joined Targeted Molecular Diagnostics in 2004 as a molecular biologist and was the Director of Molecular Biology when TMD was acquired by Quintiles. He received his PhD in Molecular Genetics from the University of Illinois at Chicago and did his post-doctoral studies at the Cleveland Clinic Foundation in 2004. Dr. Hill developed model systems for screening of chemical libraries to identify p53 modulating compounds and also to dissect the function of TopoII isoforms in drug response. A p53 activating compound that he helped characterize is currently in clinical studies. Dr. Hill currently serves as Associate Director of External Science Affairs for Quintiles Central Laboratories and uses his experience in tissue-based biomarkers to engage clinical and translational scientists in biopharma. These relationships provide a direct line of communication from our clients about current and emerging biomarker needs in oncology so that Quintiles can respond to our customers' needs now and in the future.