UNRESTRICTED EDUCATIONAL GRANT REQUEST

American Society of Clinical Oncology (ASCO) Independent Satellite Symposium

Emerging Therapy Combinations for Metastatic Breast Cancer

A 6-figure proposal; Stratamed was awarded the grant. CreateWrite also wrote the faculty content and slide deck content for the symposium.

I. Needs Assessment Summary

Treatment of metastatic breast cancer is problematic in many ways. In most cases, treatment palliates, as opposed to cures. No gold standard exists for treatment protocols. Implementation of the newest treatments available is hampered by physicians' lack of knowledge of biologics and novel targeted therapies that can be used in combination with other drugs to achieve more symptom-free time for their patients. The perception that sequential monotherapy is just as good as sequential combination therapy is fueled by scattered data that show longer times to progression, but not necessarily longer overall survival rates. However, novel targeted therapies can overcome some of the problems inherent in treating metastatic breast cancer, particularly treatment resistance. When physicians understand the dynamics of tumor evolution, they can more readily recognize the value of emerging targeted therapies, and can put that information into practice for improved patient outcomes.

II. Learning Objectives

Upon completion of this program, participants should be able to

- Discuss signaling pathways involved in metastatic breast cancer tumors
- Identify at least 5 of the newest entries in novel targeted therapies and/or biologic therapies
- Explain the rationale behind combining these therapies with other therapeutic agents
- Explore the benefits and limitations of these new combination therapies
- Examine how these combination therapies can be integrated into oncology practice

By providing examples of emerging combination treatments for metastatic breast cancer, the program aims to illustrate value of combination treatment strategy, instill confidence for adoption of combination treatment into practice, and improve patient outcomes.

III. Program/Event Description

StrataMed, LLC, in association with University of Texas M. D. Anderson Cancer Center, proposes an accredited, independent satellite dinner symposium to be held at the American Society of Clinical Oncology 2009 Annual Meeting in Orlando, Florida. The meeting will take place from May 2–June 2, 2009. The CME program will target an audience of 200 physicians and other healthcare professionals.

IV. Needs Assessment

Introduction and Background

Prevalence and incidence of metastatic breast cancer
One in 8 females in the United States will be diagnosed with breast cancer during her lifetime. An estimated 184,450 new cases of breast cancer will be diagnosed in 2008, and an estimated 40,930 people will die from breast cancer this year.[1]

When diagnosed, most people will have early-stage disease; however, 6 to 10 percent will have metastatic breast cancer (MBC) at presentation. Another 30 percent will relapse or not respond to initial treatment. The prognosis is poor for people in both of these categories; their estimated 5-year survival rate is only 21 percent.[2] For nearly all these people with MBC at presentation or relapse, today's treatments will provide palliation instead of a cure.[3]

Approximately 30 percent of breast cancer cells have an excess amount of HER2 protein (human epidermal growth factor receptor 2) on their surface, which makes such cancers more aggressive. However, when HER2+ primary tumors metastasize, they frequently no longer express this protein, which can complicate treatment. As more targeted biologic therapies become available, biopsies of metastases will provide increasingly important information regarding disease prognosis and the types of treatments that offer the greatest potential therapeutic benefits.[4]

Factors that complicate treatment choices for metastatic breast cancer
Despite the fact that oncologists now can choose from 50 therapeutic agents,[5] no gold standard exists today for treating metastatic breast cancer.[2] A dizzying array of novel treatments and biologic drugs may be used as monotherapy or in combination with one or more other agents. Many practitioners perceive that combination therapy seldom improves overall survival and frequently increases the burden of treatment on the patient. Because of their lack of confidence in newer, combination therapies, many US oncologists use sequential, single-agent chemotherapy for metastatic breast cancer.[2] An unfortunate offshoot of this is that treatment is administered according to personal preference or beliefs as opposed to being based on clinical evidence.

Because tumor response is greatest with first-line treatment (whatever is chosen),[2] treatment resistance is a key issue with metastatic breast cancer. In addition, oncologists must take into account how metastacized tumors evolve. Knowledge of the changing cell biology of tumors and how the newest therapeutics address these changes is critical for selecting the most efficacious treatments. For example, HER+ metastases that become HER- will no longer respond to trastuzumab unless that treatment is supplemented or replaced with adjuvant therapy or monotherapy, respectively. An agent such as RAD001[6] that inhibits the PI3K signaling pathway can overcome trastuzumab resistance.[7]

Additional considerations that complicate treatment decisions include the patient's age, compliance, comorbidities, previous exposure to drugs, complications from previous therapy, nodal status, tumor burden, hormone and protein receptor status, quality of life, and time to recurrence (<1 year or >1 year makes a difference in plausible treatment options). Because today's technology allows for earlier detection of tumors, patients with HER+ metastatic breast

cancer will likely already have been treated with an anthracycline, a taxane, and/or trastazumab.[2,3,8] All of these factors point to the need for individualized therapy.[3]

Prognostic indicators

Understanding critical biochemical pathways in cancer cells, including apoptosis, proliferation, angiogenesis, DNA repair, cell cycle progression, invasion and metastases, is playing an ever-increasing role in determining the best treatment options as well as their predicted outcomes. The genomic transcriptome changes throughout the course of metastatic breast cancer; the goal is to know how it changes and how treatments target various pathways, so we may predict the sensitivity and pharmacodynamics of drug response.[9]

Current treatment algorithms for HER2+ metastatic breast cancer management

Few treatment algorithms exist for metastatic breast cancer. The goal is to increase time to progression with as few toxic side effects as possible. Little evidence exists for the optimal sequence, duration, or components of therapy.[3] If the disease of patients with HER2+ has progressed after receiving trastuzumab, no clear guidelines exist for the next step. A number of new therapeutics, such as lapatinib, a tyrosine kinase inhibitor,[3] show promise; however, lapatinib is not active as monotherapy. Many clinical trials are in progress to test lapatinib with other agents.

As tumor size increases, the neoplastic and angiogenic pathways it can access broaden considerably and redundancies occur.[10] Newer biologic therapies, such as pan-HER inhibitors and heat shock protein 90 inhibitors, are in clinical trials to address such expanded tumor communication pathways.[6] The latest ASCO 2008 report lists 16 agents, most of them new, which act on multiple pathways. Most new agents, such as the epothilone ixabepilone, are being tested as adjuvants in clinical trials.[6] All of this underscores the need for education in newer treatments, their modes of action, and most importantly, how they are used in combination with other treatments.

Identification of Educational Gaps

The speed at which biologics, novel targeted agents, and combination therapies are being introduced to the market and the medical community is outpacing oncologists' prescribing practices. So physician perceptions, rather than evidence-based medicine, influence their decisions regarding treatment for metastatic breast cancer.[2] This was highlighted in an abstract presented during the ASCO 2007 Breast Cancer Symposium; a chart review of 144 patients with metastatic breast cancer who were resistant to anthracycline, taxane, and capecitabine revealed that 67 different treatment regimens were prescribed.[11] A May 2008 article in *Oncology*, which included a diagram of recommended treatments for metastatic breast cancer, mentioned only one novel targeted therapy (lapatinib) in its algorithm for HER+ disease.[3]

For the past 30 years, oncologists have known the efficacy of dose-dense chemotherapy and its positive effect on increased overall survival rates in breast cancer patients. Sequential dose-dense treatment also is widely recognized and practiced. The same cannot be said for dose-dense combination therapies. Relatively few studies have been published on sequential, dose-dense combination therapies—especially studies that include biologic drugs.[12] Many such studies are in various stages of clinical trials today, including combination therapies for HER+ metastatic breast cancer.[6]

CME offerings in the areas of metastatic breast cancer and combination drugs typically discuss one or two treatments in depth, or focus on one issue (eg, cardiovascular toxicity across one or more classes of drugs). A different approach is needed to effect positive change in discussing newer treatment options with patients and modifying prescribing practices.

This education gap can be closed by bringing together a panel of experts who can offer a "view from above" to show oncologists the newest combination treatments, explain their mechanisms of action and offer firsthand experience in using biologics and novel targeted agents. This panel can also discuss comparisons of treatment combinations, as well as treatments on the horizon. With this knowledge, physicians can expand their armamentarium of treatment options.

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