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BREAST CANCER

Advances in Treatment of Metastatic Breast Cancer: Evolving Role of the Taxanes

An interview with Peter Bjerkerot, RN, OCN
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Television specials, fundraising runs, and other special events held around the country in October marked National Breast Cancer Awareness Month. National Breast cancer is the most common type of cancer among women, other than skin cancer, and the second leading cause of cancer death for women in the United States, lung cancer being number one. Nearly all deaths from breast cancer are attributable to metastatic, or stage IV, breast cancer. It is estimated that nearly 155,000 women in the United States are currently living with metastatic breast cancer, and the number is projected to increase to nearly 162,000 by the year 2011.[1] In this interview, Peter Bjerkerot, RN, OCN, provides an overview of treatment options for metastatic breast cancer, focusing on recent advances in taxane therapy.

Continued on page 10

What are the major treatment options for metastatic breast cancer?

Surgical intervention is generally how all women enter into their journey with breast cancer. We've gotten better at screening women, educating them about the importance of doing self breast examinations and getting routine mammograms. And the technology has gotten so much better that we can pick up a lot more cases while it's still early. When breast cancer is detected early, it can usually be surgically treated, and then we follow up with chemotherapy and radiation therapy, depending on factors such as the individual characteristics of the woman and the type of tumor. When breast cancer spreads beyond the breast and lymph nodes, however, more aggressive treatment approaches are needed. There are three broad types of medical therapies for metastatic breast cancer—hormone therapy, chemotherapy, and biologic or novel targeted therapy.

How do these different types of therapies work?

Hormone therapy. Hormone therapy is generally used for women whose breast cancer expresses or overexpresses estrogen receptor or progesterone receptor positivity. In a nutshell, hormonal therapies work by blocking production of estrogen, or by sequestering the estrogen that is produced.[2] Therefore, those tumors that feed on estrogen to grow do not have an estrogen supply.

Chemotherapy. We also have a variety of chemotherapy agents, which stop growth of cancer cells, either by killing the cells or preventing them from dividing.[3] The four types most commonly used for breast cancer are the anthracyclines, alkylating agents, antimetabolites, and taxanes.

Targeted therapies. The biologic or novel targeted therapies specifically target proteins that are overexpressed in cancer cells, leading to cancer growth and spread.[4] Target therapies commonly used to treat metastatic breast cancer include agents that inhibit the activity of HER2 and those that inhibit vascular endothelial growth factor. Often, targeted therapies are given in combination with standard chemotherapy.

What are some factors to consider when selecting therapy?

We now can do more intense or in-depth analysis of the genetic makeup of the breast cancer itself to see which drug is going to be better than the other for an individual patient. You also then look into the woman's preference as far as which one she would prefer to use. That's an important part to remember—that patients have 51% of the vote.

The drugs have different side effect profiles. Some are more aggressive than others. For some, treatment time is shorter than for others. Another factor to consider is how bad the disease is. Do we just need to buy some time, or are we going to be aggressive and try to cure it?

Of course, we also have to consider that patient's underlying condition as well. It's always benefits versus risks, just like with any other form of medicine. The problem with oncology is that there are always risks. We don't give benign drugs.

Oncology has gotten to be very sophisticated in that we're looking at gene lines. We're looking at chromosomes. We really are taking huge steps forward, and it's going to continue to be that way for decades to come. It's an exciting time to be in oncology.

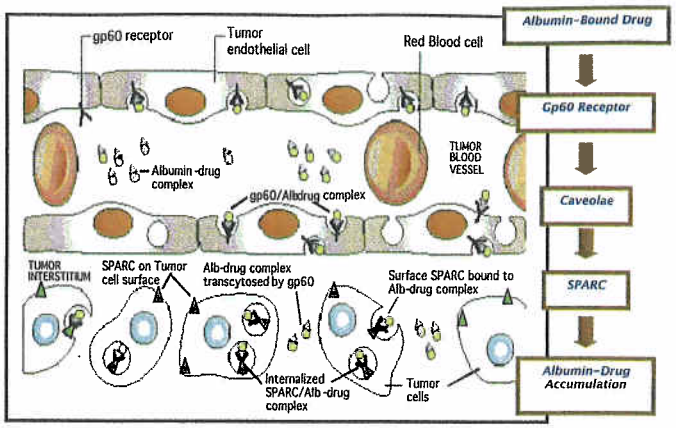

Figure. Mechanism for the transport and accumulation of nab-paclitaxel in tumors. The transcytosis of albumin-bound paclitaxel across the endothelial barrier is facilitated by the binding to the gp60 receptor and caveolar transport. In the tumor intestinal space, albumin-paclitaxel complexes bind to SPARC (secreted protein, acidic and rich in cysteine) and are rapidly internalized in tumor cells via a nonlysosomal pathway.

The taxanes paclitaxel and docetaxel are among the most widely used drugs for metastatic breast cancer, and new developments in taxane therapy have been reported recently. Could you tell us more about the evolution of taxanes and their role in treatment of metastatic breast cancer?

In 1994, solvent-based paclitaxel (Taxol), became available for treatment of breast cancer. Then, in 1996, the second taxane, docetaxel (Taxotere) was introduced. Originally, paclitaxel was approved for women with metastatic disease who had progressed through one other chemotherapy regimen or who had had chemotherapy in the adjuvant setting. If, within 6 months of stopping the chemotherapy, the patient's tumor began to grow or new lesions were found, she was able to get paclitaxel. Docetaxel was also approved for use in the adjuvant setting. Taxane-containing regimens have been shown to prolong overall survival, time to progression, and overall response in women with metastatic breast cancer; they are widely used, but there are some problems associated with their use.[5]

What are some challenges associated with taxane use?

Probably the biggest challenge is that the taxanes cannot be dissolved in water and so they have to be combined with solvents. The problem is the solvents can prolong infusion time and cause side effects beyond those caused by the drug itself.[6,7] Regardless of which solvent is used, there's a variety of side effects associated with them, such as neuropathy, neutropenia, and allergic reactions, even to the point of anaphylactic reactions, and premedication is need to prevent these hypersensitivity reactions. Sometimes therapy has to be discontinued because of side effects. With cancer therapy, basically what we do is give somebody who feels pretty good drugs that make them feel pretty bad while we're fighting their cancer. And so, it is important to try to minimize those side effects as much as possible. That was the impetus for the development of an albumin-based, solvent-free formulation of paclitaxel known as nanoparticle albumin-bound (nab)-paclictaxel (Abraxane), which was approved as monotherapy in 2005.

How does this new formulation compare with conventional taxanes?

Basically what they did was to combine the paclitaxel molecule with human albumin, which made it possible to put it into solution (Figure). That eliminated the need for the solvent, so there are no solvent-related side effects, and there is no need to premedicate patients with steroids or antihistamines to prevent hypersensitivity reactions. Also, because we've taken the solvent out and thus eliminated the solvent-related side effects, we can give about 49% more of the drug to the patient without increasing the side effects or affecting the patient's quality of life.

Another advantage is that the drug can be infused in 30 minutes compared with up to 3 hours with solvent-based paclitaxel.[8] You don't need to have intravenous tubing, which is necessary with solvent-based taxanes, because the solvents would actually leech out the plastic particles in the tubing.

You mentioned the side effects of solvents, but what about the side effects of paclitaxel itself?

The paclitaxel molecule itself does cause side effects. Neutropenia is one of them, and it can be severe. We have to watch patients closely for that, and use appropriate interventions, such as advising them to avoid crowds and take antibiotics when their blood count is low. One of the most important things we can do is to start them on bone marrow–stimulating drugs to keep their blood count up. Probably the biggest issue with paclitaxel is the neuropathies, such as numbness and tingling of the hands and feet. It may be necessary to interrupt treatment if neutropenia or neuropathy occurs. There are no evidence-based interventions for neuropathy, but there are some pharmacologic and nonpharmacologic interventions that are effective. [For a fact sheet on assessment and management of peripheral neuropathies, write to Peter. Bjerkerot@mindspring.com.]

Have there been any large clinical trials of nab-paclitaxel?

It has been studied both as monotherapy and, more recently, in combination with other agents. In two large phase 3 studies of its use as monotherapy, nab-paclitaxel without premedication was compared with solvent-based forms of paclitaxel with premedication in patients with metastatic breast cancer.[9,10] In both studies, response rate and time to tumor progression were greater in patients treated with the nab-paclitaxel regimen than with standard paclitaxel.

At the 2008 American Society of Clinical Society (ASCO) meeting, a few studies were presented of use of nab-paclitaxel in combination therapy, and the results are very promising (Sidebar).

Combination Therapy for Metastatic Breast Cancer

At the 2008 annual meeting of ASCO, Danso and colleagues reported interim results of a phase 2 study in which nab-paclitaxel was given in combination with the targeted agent bevacizumab (Avastin) as first-line treatment of metastatic HER2-negative breast cancer. In the 45 evaluable women, the overall response rate was 33%, and 18% of women had stable disease for more than 16 weeks.[11] In another ongoing study, Seidman and associates treated 30 women with HER2-positive metastatic breast cancer with nab-paclitaxel in combination with carboplatin and trastuzumab (Herceptin).[12] Of the 26 evaluable patients, 12 had a complete or partial response, and the median progression-free survival was 16 months.

What is the rationale for combining nab-paclitaxel with another agent?

To put it simply, combining drugs allows you to come at the cancer in more than one direction. With this two-pronged approach, the goal is to get more drug available to kill the cancer kill, without increasing the number or severity of side effects. The drugs have different mechanisms of action and different side effect profiles. You may see different side effects, but the severity is not going to be much greater than with either drug used individually.

The clinical trials presented at

Continued on page 12

Continued from page 10

ASCO of nab-paclitaxel combined with another agent suggest that this can be acomplished. You have to remember, however, that these were phase 2 studies with small numbers of patients, so it is hard to generalize from the results. Larger studies are needed to confirm the results, but the results so far suggest that combination therapy is a promising approach for the treatment of metastatic breast cancer.

—Karen Rosenberg

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