ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

Emerging Nontaxane Therapies for Metastatic Breast Cancer

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H&O What is the usual treatment for metastatic breast cancer?

RO The treatment decisions are based on whether the cancer is estrogen-receptor positive, HER2 positive, or triple negative. In patients with estrogen-receptor–positive cancer, very often we start with hormonal therapy. In patients with HER2-positive disease, we usually start with trastuzumab (Herceptin, Genentech) plus chemotherapy. In triple-negative disease, we start with chemotherapy, usually a taxane, particularly if the patient has not been treated in the adjuvant setting and has not received a taxane for a period of time. I tend to use single-agent paclitaxel, but docetaxel (Taxotere, Sanofi-Aventis) is also used quite widely. A patient who has received an adjuvant taxane within a year before relapse might be considered for an agent such as capecitabine (Xeloda, Genentech) as an alternative. A clinical trial is always a good option for these patients.

H&O What are the limitations to taxane therapies?

RO Although the side effect profile of these agents differs, the main concern with taxanes is neuropathy. Docetaxel has toxicities; it is associated with myelosuppression. In addition, many patients receiving docetaxel, especially long-term, tend to experience substantial fatigue. The dosing schedule of docetaxel—every 3 weeks—is a benefit. However, it is often necessary to administer growth factors with docetaxel, which I prefer not to use in the metastatic setting. Neuropathy can occur but is usually seen less often than with paclitaxel.

Paclitaxel, given on a weekly schedule for 3 of 4 weeks, is usually reasonably easy to tolerate in terms of myelosuppression and nausea. However, cumulative doses of paclitaxel lead to some degree of neuropathy in most patients. Some patients develop significant neuropathy, which can necessitate discontinuation of the agent.

Another taxane is nab-paclitaxel (Abraxane, Celgene), which essentially is a nanoparticle formulation of paclitaxel. The paclitaxel forms the core of this nanoparticle, and albumin is on the external surface. This agent takes advantage of the albumin transport mechanisms in the body. Overall, nab-paclitaxel probably results in better tumor penetration than paclitaxel. In randomized trials, nab-paclitaxel has been shown to be superior to paclitaxel. Typically, it is given weekly, 3 weeks out of 4. It does not cause much myelosuppression, but, again, it can cause neuropathy.

H&O What are some of the emerging nontaxane therapies?

RO We have had trastuzumab and lapatinib (Tykerb, GlaxoSmithKline) for several years now, and there are a number of new agents in development. Pertuzumab (Omnitarg, Genentech/Roche) is an antibody that targets the HER2 receptor, but in a different domain than

trastuzumab, and it has been shown to have efficacy when given in combination with trastuzumab and chemotherapy. Trastuzumab emtansine (also known as T-DM1, Genentech/Roche) is a conjugate of trastuzumab and a chemotherapy moiety; randomized data on this agent will be available later this year. The mammalian target of rapamycin (mTOR) inhibitor everolimus (Afinitor, Novartis) has been shown to improve outcomes for patients with hormone-receptor–positive breast cancer that has become resistant to hormonal therapy. There are also data with this drug in HER2-positive cancers in patients who have cancers resistant to trastuzumab.

As for chemotherapy, a number of drugs—including capecitabine, gemcitabine (Gemzar, Lilly), and vinorelbine—have been used in breast cancer for quite some time. Recently, new agents have been developed specifically for patients who had developed resistance to standard taxane therapy. The first one is ixabepilone (Ixempra, Bristol-Myers Squibb), which, again, targets the microtubule, but differs from standard taxanes in that it is effective in cancers that have become resistant to paclitaxel or docetaxel. It is usually given as a single agent once weekly, usually 3 weeks out of 4, or it can be administered every 3 weeks. Similar to standard taxanes, ixabepilone has been associated with neuropathy. In a randomized trial comparing ixabepilone plus capecitabine versus capecitabine alone, the combination resulted in improved progression-free survival in patients with cancers that were resistant to both anthracyclines and to taxanes. This finding represents a meaningful improvement in outcome. Additionally, the ixabepilone/capecitabine combination achieved responses in about a third of patients with triple-negative breast cancer, even though these patients had received prior anthracyclines and prior taxanes. These patients typically do not have many options, so these data are interesting.

The second drug is eribulin (Halaven, Eisai), which also targets microtubules, although in a different manner compared to the standard taxane and ixabepilone. Similar to ixabepilone, eribulin has been shown to be effective in preclinical models of patients who are resistant to standard taxanes. The US Food and Drug Administration (FDA) approved eribulin in November 2010, based on the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin) trial, which had an interesting design. Patients who had received several lines of prior chemotherapy in the metastatic setting were randomized to either eribulin (given on days 1 and 8, every 3 weeks) or to the physician's choice of any single-agent therapy, including single-agent chemotherapy, hormonal therapy, or a targeted agent. In 95% of cases, the choice was for single-agent chemotherapy. The patients in this study were heavily pretreated; they had received a median of 4 prior lines of chemotherapy in the metastatic setting. The trial showed that the use of eribulin significantly improved overall survival, which was the primary endpoint, compared to the monotherapy that the physicians had selected. Eribulin has been used in heavily pretreated patients, and there is interest in studying it in patients who have received fewer courses of prior therapy.

Eribulin has been associated with neuropathy and myelosuppression, which can result in the need for treatment adjustments. However, I think some of the myelosuppression can be explained by the fact that the agent is being used in patients who have had multiple lines of prior chemotherapy and thus much less bone marrow reserve than patients in a first-line or second-line setting.

H&O Are there certain types of patients who are likely to benefit from nontaxane therapy?

RO Patients likely to benefit from nontaxane therapy are those who experience significant adverse events or disease progression while receiving taxanes. For example, in a patient who develops neuropathy from paclitaxel or docetaxel, capecitabine or gemcitabine might be good options. Among patients who either did not benefit from the standard taxane or benefited and then experienced disease progression—which will be most patients—the use of ixabepilone or eribulin is justified. The question is whether novel microtubule agents like ixabepilone and eribulin are going to be more effective in earlier lines of therapy. Data on this topic are currently limited.

H&O Are nontaxane therapies used as single agents or as part of combination therapies?

RO These therapies are used both as single agents and, with the exception of eribulin, in combination regimens. Capecitabine is very commonly used as a single agent or, less frequently, with ixabepilone. It has also been used with docetaxel, but this regimen can have substantial toxicities. Ixabepilone is also used as a single agent and, as mentioned, with capecitabine. The only data we have for eribulin are as a single agent. Gemcitabine is used as a single agent or with paclitaxel. Vinorelbine is usually used as a single agent, but again, it can be used in combination with other chemotherapy agents.

There is an ongoing debate about which patients need combination therapy and which patients need single-agent therapy. Trials have not really addressed this question. Most physicians would prefer the use of sequential single agents because this approach is less toxic as compared with combination therapy. However, combination therapy is appropriate for certain patients, such as those who have a high metastatic load or many liver metastases.

H&O What are some areas of research?

RO Much of the current research is focused on breast cancer subtypes. There is much interest in finding therapies that can be effective in hormone-resistant metastatic breast cancer. In the HER2-positive setting, there is research to find therapies for patients who no longer benefit from trastuzumab or lapatinib.

Among the nontaxane chemotherapies, there are trials examining eribulin in patients with metastatic disease who had received no prior chemotherapy or just 1 line of chemotherapy. Other research is examining eribulin and ixabepilone in the early-stage setting, particularly in patients who received preoperative chemotherapy, in whom treatment can be adjusted based on the response.

Researchers also aim to determine why a certain patient's cancer might respond to one of these agents but not another. What is the molecular profile that is associated with resistance versus sensitivity? An understanding of that response could allow us to make these drugs work better, and perhaps find other effective agents for patients who do not respond to existing ones.

Suggested Readings

Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-923.

Gradishar WJ, Krasnojon D, Cheporov SV, et al. Albumin-bound paclitaxel (abpac) versus docetaxel for first-line treatment of metastatic breast cancer (MBC): final overall survival (OS) analysis of a randomized phase II trial. *J Clin Oncol* (ASCO Breast Cancer Symposium Abstracts). 2011;29(suppl 27). Abstract 275.

Rugo HS, Roche H, Thomas E, et al. Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. Poster presented at the San Antonio Breast Cancer Symposium; December 12, 2008; San Antonio, TX. Poster 3057.

Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol*. 2010;28:3256-3263.