ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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The Role of Albumin-Bound Paclitaxel in Metastatic Breast Cancer

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H&O What is albumin-bound paclitaxel and how does it differ from traditional taxanes?

CR Paclitaxel is very hydrophobic, meaning it does not go into solution easily. Thus, standard paclitaxel has had to be put into solution with a vehicle called cremophor. Cremophor is associated with hypersensitivity reactions; it can encapsulate the paclitaxel so that it is not fully available once it goes into solution, and probably adds to the neutropenia and neuropathy that is seen with the drug. Because of this and other associated toxicities with cremophor, a nanoparticle albumin-bound paclitaxel (Abraxane, Celgene) was developed. The albumin envelops the paclitaxel molecule and renders it hydrophilic. The albumin is a carrier of nutrients, and is able to easily move into cells through a mechanism of albumin receptors. Albumin-bound paclitaxel has the ability to easily put paclitaxel into solution and therefore avoid some of the toxicities seen with cremophor. Docetaxel, another taxane, is also bound to a vehicle that is called tween 80; it is associated with some lesser toxicities than cremophor, but still adds to the hypersensitivity reactions that are seen with that taxane. There are currently technologic attempts being made to create a nanoparticle albumin-bound docetaxel.

H&O What studies have demonstrated the efficacy of albumin-bound paclitaxel as a single-agent in metastatic breast cancer?

CR The original studies were phase I dose-finding trials. One dose-finding trial enrolled 19 patients, none of whom required steroid premedication, as is required with cremophor paclitaxel. The maximum tolerated dose (MTD) in this trial was 300 mg/m^2. Two different phase II studies were subsequently undertaken; one evaluated nanoparticle albumin-bound paclitaxel at a dose of 175 mg/m^2, which is the standard paclitaxel dose. The response rate seen in the 41 patients enrolled in this study was 40%; in patients who were chemotherapy-naïve, the response rate was 45%. The second phase II trial evaluated albumin-bound paclitaxel at a dose of 300 mg/m^2. This study enrolled 59 patients and demonstrated a response rate of 48%; frontline patients had a response rate of 64%. A fairly significant amount of neuropathy was seen with this higher dose.

The dose was then reduced to 260 mg/m^2 and studied in a phase III trial of 460 patients. This study randomly assigned patients with metastatic breast cancer to either albumin-bound paclitaxel at a dose of 260 mg/m^2 every 3 weeks or to cremophor-based paclitaxel at 175 mg/m^2 every 3 weeks (although this is the US Food and Drug Administration-approved schedule, most oncologists administer paclitaxel in a weekly setting). The primary study objective was response rate, and secondary objectives included time to tumor progression and survival. Exclusion criteria included prior taxane use for metastatic breast cancer; the median age was 53 years. Approximately 40% of patients had received 1 prior chemotherapy regimen in the metastatic setting, and about 40% did not have any prior chemotherapy. The findings from this study, authored by Dr. William Gradishar in the *Journal of Clinical Oncology* in 2005, showed that the response rate was nearly doubled from 11.1% in patients who received

cremophor-based paclitaxel versus 21.5% for patients who received albumin-bound paclitaxel. In patients who had recently failed prior chemotherapy, the response rate was also doubled from 8.4% to 15.5%. Safety was more favorable with albumin-bound paclitaxel; neutropenia occurred more frequently with cremophor-based paclitaxel than with albumin-bound paclitaxel even though the dose was substantially higher for the albumin-bound formulation. Neuropathy was higher in the albumin-bound paclitaxel patients; however, these patients received a significantly higher dose during each administration and were treated longer because they took longer to demonstrate disease progression on the drug. This trial was the basis for the FDA approval of albumin-bound paclitaxel for metastatic breast cancer.

In the interim, there were several randomized trials evaluating the optimal schedule of cremophor-based paclitaxel. These trials have suggested that weekly administration is more efficacious than every-3-week administration. None of these trials were conducted in an attempt to get approval for weekly paclitaxel administration; however, weekly paclitaxel eventually became the standard of care in the metastatic setting. Because of this new standard of care, it was necessary to do trials looking at weekly albumin-bound paclitaxel, as it was difficult to compare weekly cremophor-based paclitaxel to every-3-week albumin-bound paclitaxel. In order to determine the optimal weekly dosing, investigators went back and conducted phase I and II trials with weekly albumin-bound paclitaxel. A phase I dose-finding study found that if patients were lightly pretreated, the MTD was 150 mg/m^2 weekly; in heavily pretreated patients, the MTD was 100 mg/m^2 weekly. Neuropathy was commonly reported in the albumin-bound paclitaxel patients. Subsequently, phase II trials enrolled patients who were heavily pretreated and taxane refractory; 1 study evaluated a dose of 100 mg/m^2 and a second study looked at a dose of 125 mg/m^2 weekly. Both studies had significant response rates and tolerable safety profiles.

The next comparator trial was a randomized phase II trial that evaluated different doses and schedules of the taxanes docetaxel and albumin-bound paclitaxel. The 4 arms of the trial were weekly albumin-bound paclitaxel (100 mg/m^2, 3 out of 4 weeks and 150 mg/m^2 3 out of 4 weeks), every-3-week albumin-bound paclitaxel (300 mg/m^2 until progression), and docetaxel (100 mg/m^2 every 3 weeks). A total of 300 patients were enrolled, 75 patients per arm. The objectives of the study were to compare any of the albumin-bound paclitaxel arms to docetaxel, weekly versus every-3-week administration of albumin-bound paclitaxel, and low-dose versus high-dose weekly albumin-bound paclitaxel. The findings showed that response rates were best for weekly albumin-bound paclitaxel (63% for 100 mg/m^2 and 74% for 150 mg/m^2); the response rate for 300 mg/m^2 albumin-bound paclitaxel every 3 weeks was 46%, and it was 39% for docetaxel. These data were published in the *Journal of Clinical Oncology* in 2009, with Dr. Gradishar as first author. As a result, it was recognized that albumin-bound paclitaxel given on a weekly schedule was likely superior to every-3-week albumin-bound paclitaxel.

H&O What is the design of the ongoing CALGB 40502 study, and what are the potential implications of this study?

CR The Cancer and Leukemia Group B is conducting a phase III trial in patients with locally recurrent or metastatic breast cancer. There are 3 chemotherapy comparison arms being evaluated in the trial: paclitaxel 90 mg/m^2 weekly 3 out of 4 weeks versus albumin-bound paclitaxel 150 mg/m^2 3 weeks out of 4, versus ixabepilone delivered 3 weeks out of 4. Prior to randomization, investigators have the option of adding bevacizumab (Avastin, Genentech) to the treatment arm. It is anticipated that 900 women will be enrolled in the trial. Patients are allowed to have received prior adjuvant or neoadjuvant taxanes, but are not allowed to have any prior chemotherapy for metastatic breast cancer. I think the findings from this study will help us better understand whether there is an advantage to nanoparticle technology, particularly for albumin-bound paclitaxel given in its most efficacious manner, which is weekly at 150 mg/m^2 in patients without prior chemotherapy in the metastatic setting.

H&O In which patients do you consider albumin-bound paclitaxel as the taxane of choice for single-agent therapy?

CR Albumin-bound paclitaxel given weekly is my standard frontline taxane of choice for most patients with metastatic breast cancer. I believe that, at least in the weekly dosing schedule, it is more efficacious and is much safer in that we are able to prevent the use of steroids and other premedications. Patients are able to receive albumin-bound paclitaxel over a much more rapid infusion time, and cost analyses comparing cremophor-based paclitaxel and albumin-bound paclitaxel have shown that it is more cost-effective to use albumin-bound paclitaxel.

H&O In which patients would you consider albumin-bound paclitaxel as a combination partner?

CR I have been using bevacizumab with albumin-bound paclitaxel in the metastatic setting. The CALGB 40502 trial will study this combination formally, otherwise it has only been evaluated in multiple relatively small phase II

trials, which showed expected safety with the combination. In patients with metastatic, HER2-positive breast cancer, I use albumin-bound paclitaxel with trastuzumab (Herceptin, Genentech). This drug is easily combinable with biologic agents with only minimal enhancement of toxicity or problems therein. Albumin-bound paclitaxel is a particularly well-suited drug when administered with an antibody such as trastuzumab, because we can eliminate steroid use and potential complications caused by poor immune response.

H&O What albumin-bound paclitaxel combination regimens are being explored?

CR There are no formal phase III trials that have looked at combinations. All of the trials that have been published to this point are relatively small phase II trials, and the dosing is inconsistent. Albumin-bound paclitaxel can be combined with a platinum and with gemcitabine. However, I do not think we have a great understanding of the appropriate dosing of albumin-bound paclitaxel when using it as a combination partner.

There have been numerous reports of combining albumin-bound paclitaxel with carboplatin and bevacizumab, especially in the neoadjuvant setting. Some of the endpoints of these trials are looking at SPARC expression to determine whether SPARC is predictive of benefit. Ongoing studies are trying to establish optimal dosing for albumin-bound paclitaxel in combination.

Suggested Readings

Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23:7794-7803.

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Lobo C, Lopes G, Baez O, et al. Final results of a phase II study of nab-paclitaxel, bevacizumab, and gemcitabine as first-line therapy for patients with HER2-negative metastatic breast cancer. *Breast Cancer Res Treat*. 2010;123:427-435.