

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Chemotherapy Regimens in Metastatic Breast Cancer

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H&O Can you talk about the different types of chemotherapy regimens?

SG It is first necessary to understand that different subtypes of breast cancer require slightly different chemotherapy regimens. The main example is HER2-positive breast cancer versus triple negative breast cancer. These subtypes correlate with unique gene profiling, phenotypes, and clinical outcomes. So, the most important factor in the decision-making process is cancer subtype.

Once cancer subtype is established, appropriate therapy can then be administered. In patients who have metastatic disease that is estrogen receptor (ER)-positive and progesterone receptor (PR)-positive or -negative, one should first exhaust hormonal antiestrogen treatment. If the patient does not respond to the hormonal treatment or if her cancer is extremely fast growing, there is then an indication for chemotherapy, although it is still not 100% clear which chemotherapy treatment is best. Another subtype of breast cancer is HER2-positive disease. This entity has revolutionized how we think of breast cancer; in the last 20 years, we not only discovered a target (HER2) but also a drug that is tailored to this target (trastuzumab [Herceptin, Genentech]). The discovery of trastuzumab was followed by the development of similar agents like lapatinib (Tykerb, GlaxoSmithKline) and numerous others that are now in clinical development. We learned that treatment for HER2-positive disease should always include at least 1 anti-HER2 compound, such as trastu-

zumab or lapatinib or combinations of these agents and newer anti-HER2 compounds. However, anti-HER2 compounds should never be administered alone. We usually start with 1 or 2 such drugs and add a compound as necessary; that can include chemotherapy, hormone therapy, or antiangiogenic compounds.

The third of the many subtypes of breast cancer is triple negative breast cancer. The treatment decision-making process is easiest for this subtype because we do not use any antiestrogen or anti-HER2 treatments. Women with triple negative breast cancer are treated with chemotherapy. This subtype is usually aggressive and fast growing and, therefore, it may be necessary to use 2 or even 3 drugs in order for the patient to achieve some type of relief.

H&O Which combinations are most effective?

SG We do not have well designed, randomized, phase III studies to claim one regimen is better than another. We only have studies showing that 1 drug is not as effective as 2 drugs, or that 3 drugs might be better than 2, but we do not have comparative studies to show superiority of one particular combination over another.

In ER-positive tumors, which tend to be less aggressive, the ideal treatment starts with hormone therapy. If that is exhausted, patients should then be given oral drugs such as capecitabine, because they have shown a good response. The median duration of response in these patients is up to 6–8 months.

In triple negative breast cancer, use of capecitabine is not as effective and therefore rarely used. In HER2-positive breast cancer, capecitabine is one of the possible compounds combined with anti-HER2 treatments (Geyer and colleagues published a pivotal study of lapatinib plus capecitabine in second-line therapy that led to the approval of lapatinib). Once capecitabine loses efficacy or if the tumor is very aggressive (even in ER-positive tumors), the best option is taxanes, followed by other cytotoxic drugs, such as gemcitabine, ixabepilone (Ixempra, Bristol-Myers Squibb), or eribulin (Halaven, Eisai). The latter 2 agents are more frequently used in the second- or third-line setting. Taxanes are best used as frontline treatment in

metastatic breast cancer. It is important to not administer the same taxanes that the patient has been exposed to in the neoadjuvant or adjuvant setting.

In my experience, if there is a response to single-agent capecitabine, I do not add any other agent. In cases where it is necessary for the patient to have a quick and sustained response, I combine capecitabine with docetaxel (based on phase III data). Alternatively, it is possible to combine docetaxel with gemcitabine or even paclitaxel with gemcitabine (solvent-based or nab formulation), or any of the above with bevacizumab (Avastin, Genentech). At present, there is a controversy with bevacizumab, because in combination with single agents, it did not show survival benefit, but did have some progression-free survival benefit. The US Food and Drug Administration is currently reviewing its indication, whereas the European Medicines Agency continues to approve bevacizumab in combination with paclitaxel as given in the Eastern Cooperative Oncology Group E2100 study.

Platinum compounds are also extremely effective in breast cancer. However, because we did not have antiemetics and supportive care at the time when these drugs were developed, their use was limited in the past. Currently, it is easier to deal with the side effects of platinum therapy, and they are being used more effectively. Platinums are probably most effective in triple negative breast cancers. Since we do not have randomized phase III trials that compared platinum versus no platinum, we cannot say that platinums are the best option in this subgroup, but some studies hint to the fact that they are.

In general, the more aggressive the cancer, the more agents should be combined. In less aggressive and less extensive disease (eg, 5 or 6 bone metastases, some pain), I would give only single-drug therapy.

H&O What are the challenges seen with combination chemotherapy, and are there any benefits to combination therapy versus single agent therapy?

SG The main challenge is toxicity. Because we do not cure patients, it is best not to expose them to extensive toxicity. Metastatic patients have a life expectancy of approximately 2 years, so each day that they experience side effects from chemotherapy is a day with decreased quality of life.

If the patient is having lots of trouble with her cancer, then giving combination therapy may override her cancer symptoms, and she may feel better in spite of toxicity. If she does not have many symptoms (eg, very small liver or lung metastases), then she does not even feel that she has metastatic disease. In such a patient, the benefits of combination therapy may not outweigh the toxicities.

H&O What is the optimal duration of first-line therapy?

SG The optimal duration would be A) as long as the drug works and B) does so with acceptable or little toxicity. Treatment should be discontinued when the drug fails or causes substantial toxicity. Sometimes, it is possible to do away with the toxicity by reducing the dose, but this might lead to reduced efficacy. In order to avoid toxicity, switching from combination therapy to single-agent therapy is also possible. For example, if a patient has lung and liver metastases, she may be treated with 2 agents or even triplet therapy; as the cancer responds and she starts to feel better, the most toxic component of the combination may be dropped and the less toxic one continued.

H&O What are some exciting areas of research?

SG There are several exciting areas of development. In the ER-positive breast cancer group and some subtypes of ER-positive and HER2-positive cancer, there are now 2 studies that show that combining antiestrogen and anti-HER2 agents is better than using either alone. This is exciting because we are able to delay chemotherapy for 6–8 months. The second area with exciting data is in HER2-positive patients. We are testing various compounds: neratinib (Pfizer), trastuzumab DM1 (Genentech/ImmunoGen), and pertuzumab (Roche/Genentech), and we have 2 ongoing studies at the University of Miami (one in the second-line setting and one in the first-line setting). These are potential drugs that in the future may improve outcomes in HER2-positive disease. In the triple negative breast cancer subtype, the most exciting agents are poly(ADP-ribose) polymerase inhibitors. There are 7 companies testing different formulations of PARP inhibitors.

Another area of development is the insulin-like growth factor (IGF) inhibitors. Inhibiting IGF has the potential to reverse resistance. We have also discovered that each cancer has a stem cell, and that there are some targets in this area that are “druggable,” meaning we can create a drug against them. Numerous other agents are being studied as well, including PI3-kinases, sarcoma inhibitors, adenosine triphosphate inhibitors, MET inhibitors, and mammalian target of rapamycin inhibitors.

Suggested Readings

Gianni L, Pienkowski T, Im Y-H, et al. Neoadjuvant pertuzumab (P) and trastuzumab (H): antitumor and safety analysis of a randomized phase II study (‘NeoSphere’). Paper presented at: San Antonio Breast Cancer Symposium; December 10, 2010; San Antonio, TX.

Schwartzberg LS, Franco SX, Florance A. Lapatinib plus letrozole as first-line therapy for HER2+ hormone receptor–positive metastatic breast cancer. *Oncologist*. 2010;15:122-129.