ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Breast Cancer In Focus

Update on Administration of Adjuvant Trastuzumab

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H&O What factors are considered when deciding whether to initiate adjuvant trastuzumab?

HM Adjuvant therapy recommendations are based on individual risk-benefit calculations. For example, a person with a poor prognosis because of other comorbid conditions may not be a suitable candidate for any adjuvant chemotherapy or targeted therapy. In the absence of significant contraindications, adjuvant trastuzumab (Herceptin, Genentech) with chemotherapy is typically recommended for most women with HER2-positive (3+ by immunohistochemistry and/or ≥2 by fluorescence in situ hybridization) early-stage breast cancer as a result of the significant and consistent survival benefits demonstrated across the key adjuvant trastuzumab studies. Women with HER2-normal breast cancer are not appropriate candidates for trastuzumab-based therapy outside of a clinical study. Trastuzumab is currently approved by the US Food and Drug Administration (FDA) for the treatment of women with HER2-positive, node-positive, or high-risk (ie, hormone receptor–negative or hormone receptor–positive, tumor size >2 cm), node-negative early-stage breast cancer. Because women with lower-risk, small, node-negative, HER2-positive breast cancer were not eligible for the pivotal trastuzumab studies, the potential benefits in this population have not been prospectively studied. However, a retrospective study conducted at our institution indicates that even these lower-risk patients derive benefit from trastuzumab with chemotherapy. Because there is a small but significant risk of trastuzumab-mediated cardiotoxicity, manifesting primarily as congestive heart failure (CHF), women who have significant risk factors for CHF such as advanced age, poorly controlled hypertension, and/or a significant cardiac history may not be appropriate candidates for therapy. Notably, however, trastuzumab-mediated cardiotoxicity is typically reversible, and most women can be successfully re-challenged with trastuzumab and complete the planned course of therapy.

H&O How do clinicians decide between increased benefits and possible cardiotoxicity?

HM The significant and consistent benefits observed with the addition of trastuzumab to chemotherapy across several large randomized trials indicate that from a public health perspective, the number of lives saved with adjuvant trastuzumab administration significantly outweighs the low risk of reversible cardiotoxicity overall. However, clinicians must weigh individual patient- and tumor-specific characteristics with the expected benefits of therapy, thereby tailoring adjuvant recommendations to the individual. For example, an elderly woman with pre-existing CHF and a very small, node-negative, HER2-overexpressing breast cancer with otherwise low-risk features may not be an appropriate candidate for trastuzumab-based therapy.

H&O What evidence led to the determination that adjuvant trastuzumab may not be a good option for some women?

HM The first randomized, phase III, multicenter adjuvant trastuzumab studies were reported in 2005. In the HERA (Herceptin Adjuvant) trial, more than 5,000 women were randomized to receive trastuzumab or no trastuzumab after

completion of chemotherapy. In the combined analysis of 2 North American studies, more than 5,000 women were randomized to trastuzumab administered concurrently with chemotherapy or not. Both the HERA trial and the combined analysis demonstrated significant improvements in disease-free survival and ultimately overall survival. Notably, these adjuvant studies were undertaken with strict cardiac monitoring strategies as a result of the significant risk of CHF observed in the metastatic setting, particularly when trastuzumab was co-administered with an anthracycline. However, because different monitoring strategies and definitions were used in these studies, cross-study comparisons should be discouraged, and it has been difficult to refine the estimated rate of clinically significant trastuzumab-mediated cardiotoxicity. For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 study, 4.1% of trastuzumab-treated patients experienced a "cardiac event" versus 0.8% in the chemotherapy-alone arm. In the HERA trial, severe cardiotoxicity developed in 0.5% of trastuzumab-treated women, although notably, the only cardiac-related death occurred in the observation arm. Whether changes in left ventricular ejection fraction on frequent serial cardiac imaging correlate with significant outcomes is unknown. At this time, specific populations at risk of trastuzumab-mediated toxicity have not yet been clearly identified, and the optimal cardiac monitoring strategy is unknown.

H&O What is the optimal duration of trastuzumab administration?

HM At present, the optimal duration of adjuvant trastuzumab therapy is uncertain. In the HERA trial, for example, women who completed adjuvant chemotherapy (sequential administration) were randomized to observation, 1 year of trastuzumab, or 2 years of trastuzumab. The results presented to date compare the observation arm with the 1-year of trastuzumab arm, with significant benefits demonstrated in favor of 1 year of trastuzumab. However, because the results from the 2-year trastuzumab arm have not yet been reported, it is unknown whether any additional benefits are conferred with trastuzumab therapy extended to 2 years. Given the time that has elapsed since the reporting of the 1-year versus observation arms, it is possible that there is no significant difference between the 1- and 2-year arms, but this has yet to be confirmed.

Another interesting question is whether less than 1 year of trastuzumab therapy is adequate. In a smaller FinHer (Finland Herceptin) study, 1,000 women were randomized to receive chemotherapy with or without 9 weeks of concurrent trastuzumab. Interestingly, the benefits associated with trastuzumab administration were consistent with those observed in the larger randomized trials evaluating 1 year of adjuvant trastuzumab. As a result, the optimal duration of trastuzumab therapy is likely between 9 and 52 weeks, but it has yet to be refined. In clinical practice, most clinicians recommend a 1-year course of trastuzumab as was administered in the largest clinical trials. Occasionally, treatment is interrupted or delayed, and for some, completion of the planned duration is not possible. Typically, if a patient has an interruption or delay in trastuzumab therapy because of asymptomatic ejection fraction declines, but the ejection fraction recovers off-therapy, trastuzumab is then re-instituted with the intention of completing the planned 1-year course of therapy.

H&O Have differences between sequential and concurrent administration been observed?

HM Sequential and concurrent trastuzumab administration have not been evaluated in a head-to-head comparison. The HERA trial studied a sequential strategy of chemotherapy followed by trastuzumab or observation with significant disease-free survival and overall survival benefits observed in favor of sequential trastuzumab. In the North American studies, trastuzumab was administered concurrently with chemotherapy and as monotherapy thereafter for a total 1-year course of therapy. Although cross-study comparisons should be discouraged, it is notable that the reported benefits were similar for the sequential and concurrent strategies. However, evidence from the metastatic setting indicates that trastuzumab may be more effective when administered concurrently with certain chemotherapeutics such as taxanes. At Memorial Sloan-Kettering Cancer Center, we typically initiate trastuzumab concurrently with adjuvant, every 2-weekly (dose-dense) chemotherapy, and continue trastuzumab as monotherapy thereafter for a total 1-year course of trastuzumab therapy.

H&O What are the options for patients in whom trastuzumab is not recommended?

HM Specific options would depend on the nature of the contraindications. For example, if a woman were ineligible for adjuvant trastuzumab because of a significant history of CHF, an anthracycline-based chemotherapy recommendation is likely inappropriate given the potential for irreversible cardiotoxicity. Notably, trastuzumab is the only HER2-targeted agent currently FDA-approved in the adjuvant setting. Lapatinib (Tykerb, GlaxoSmithKline), a tyrosine kinase molecule that targets HER1 and HER2, is approved in the metastatic setting, but is still being evaluated in the adjuvant setting.

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H&O What are some of the recent data concerning adjuvant therapy in HER2-positive breast cancer?

HM There are many promising HER2-targeted drugs under development including lapatinib and other tyrosine kinase inhibitors, monoclonal antibodies including pertuzumab (Omnitarg, Genentech), drug conjugates including T-DM1 (trastuzumab-DM1), and heat shock protein 90 (Hsp90) inhibitors, many of which have been developed by colleagues at Memorial Sloan-Kettering Cancer Center. For example, after lapatinib demonstrated benefits when administered in combination with chemotherapy in the metastatic setting, a phase II study of adjuvant chemotherapy with trastuzumab and lapatinib was undertaken. However, an unacceptable rate of diarrhea was reported; and these findings were instrumental in informing the ongoing, randomized, phase III ALLTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) study. The ALLTO study is a large, randomized trial evaluating lapatinib alone versus trastuzumab alone versus sequential trastuzumab-lapatinib versus concurrent trastuzumab-lapatinib in the adjuvant setting.

A number of HER2-targeted agents have also recently demonstrated promising activity in the metastatic setting and will likely move into the adjuvant setting. Pertuzumab is a humanized monoclonal antibody that binds to HER2 but at a site distinct from trastuzumab; it has shown significant response rates when administered with a taxane in the metastatic setting. T-DM1 is a drug that links trastuzumab with a chemotherapy agent, maytansine (DM1), and has demonstrated impressive activity in trastuzumab-pretreated women with metastatic breast cancer. Hsp90 inhibitors are involved in the folding and unfolding of proteins including HER2, and have shown significant responses in the metastatic setting. Adjuvant studies incorporating these drugs are anticipated. However, because there are so many promising HER2-targeted therapies under development, a significant future challenge will be to determine the optimal combination or sequence of these agents.

Suggested Readings

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