Controlling Spiraling Costs of Cancer Called Moral Imperative

BY PEGGY EASTMAN

Holding down costs is both a professional and moral responsibility, said speakers at an Institute of Medicine National Cancer Policy Forum meeting on delivering affordable cancer care while improving quality.

Page 18
Breast Cancer: Long-Term Data from Trastuzumab Trial Give Guidance for Calculating Cardiotoxicity Risk

BY TED BOSWORTH

Better models to predict cardiac damage from adjuvant trastuzumab after an anthracycline-based therapy in HER2-positive breast cancer have been generated by seven-year follow-up from the National Surgical Adjuvant Breast and Bowel Project B-31 trial. These data, now available online ahead of print in the Journal of Clinical Oncology (doi: 10.1200/JCO.2011.40.0010), show that:

- late cardiac events are uncommon;
- impaired left ventricular function at least partially recovers in many patients after trastuzumab is stopped; and
- the risk of cardiac events appears concentrated in identifiable subgroups, particularly those who already have a low normal left ventricular ejection fraction (LVEF), women who are older than age 50, and women with hypertension.

These findings provide at least some guidance for calculating a risk-to-benefit ratio for trastuzumab after an anthracycline-based regimen in women with primary HER2-positive breast cancer, the researchers said. Based on the findings, they created an equation with which to derive a Cardiac Risk Score in patients who are candidates to receive trastuzumab therapy.

The study’s lead author, Edward H. Romond, MD, Professor in the Division of Medical Oncology at the University of Kentucky, cautioned, though, that the model may prove useful for assessing many patients, but the important point to remember is that, regardless of the choice of chemotherapy regimen, cardiac monitoring is integral to the use of trastuzumab. The equation proposed by the study’s lead authors was shown both clinically and by follow-up multiple-gated acquisition (MUGA) scans, specifically, of 37 evaluable patients in the trastuzumab group with a cardiac event, 33 had no symptoms six months after stopping trastuzumab. And although one patient in this group did die of congestive heart failure during the course of treatment, the follow-up MUGA scans demonstrated that LVEF had climbed above 50 percent in 21 patients.

It is well known, he noted, that the cardiac safety of trastuzumab, particularly when administered after exposure to an anthracycline, has been a cause of concern with the use of this agent in the treatment of patients with primary HER2-positive breast cancers. And despite abundant evidence that adjuvant trastuzumab, particularly after anthracycline-based chemotherapy, substantially reduces the risk of recurrence, the cardiac toxicity has created uncertainty about the risk-to-benefit ratio.

Accompanying Editorial

Writing in an accompanying editorial (DOI:10.1200/JCO.2012.44.9611), Erica L. Mayer, MD, MPH, and Nancy U. Lin, MD, both of Dana-Farber Cancer Institute, said that use of anthracycline-based trastuzumab regimens in HER2-positive breast malignancies has declined “precipitously” over the past several years, a likely reflection of this uncertainty.

As asked to comment on the clinical significance of the new B-31 data, Mayer said she hoped the safety information will help clinicians and patients reconsider the use of anthracycline-containing regimens, particularly in patients with a moderate-to-high risk of relapse.

And, based on the findings indicating that the risks of clinically significant cardiac toxicity are “quite low for many patients,” the lead author hoped that new data will provide at least some useful guidance for calculating many patients who are candidates to receive trastuzumab therapy.

The scoring system proposed by the B-31 investigators was derived from a regression analysis that found that only age and baseline LVEF were significant predictors of a cardiac event. When age younger than 50 was used as the index for comparison, the hazard ratio for having a cardiac event among patients age 50 to 59 was 2.43 and climbed to 2.73 for those 60 and older.

The hazard ratio climbed to 6.72 in those with LVEF that was 50 to 54 percent compared with those with LVEF of 65 percent or higher. The equation producing the score on the basis of these risk factors indicated that the risk of a cardiac event is concentrated in older patients with low normal LVEF although other factors may be important in individual patients, the researchers said.

continued on page 23

post-surgery pathology report indicated that she still had T3 disease, with a 5 cm tumor remaining. When Telli requested a second pathology review, the pathologist reported that most of the tumor bed was scar tissue with only one percent cellularity. Putting that information into the risk calculator, the patient was put into the low-risk category with minimal residual disease, RCB-1.

“I think the point that needs to be made is that in this study, the patients with RCB-1, minimal residual disease, do have the same favorable prognosis as those who have an RCB of 0 [complete pathological response],” she said.

“I think size does matter, but so do other factors, including percent cellularity and nodal status,” she concluded. “I think these do need to be considered when thinking about prognosis in these patients.”

---TRIPLE-NEGATIVE

continued from page 20
Breast Cancer Bone Metastases: Progress Toward Identifying Patients at Risk

BY RABIYA S. TUMA, PHD

SAN FRANCISCO—Women whose primary breast tumors express higher levels of RANK (receptor activator of nuclear factor kappa-B) may be at higher risk of relapse and bone metastases, compared with women whose tumors express less of the protein, researchers reported here at the Breast Cancer Symposium. Two other studies suggest that everolimus-exemestane therapy may reduce the risk of bone metastases compared with exemestane alone, and that statin use may be associated with a reduction in risk of bone metastases in breast cancer patients.

RANK Ligand as Predictor of Risk

In a study of 149 women who took part in the ISPY-1 trial (Abstract 2), Jiali Li, MD, PhD, Clinical Instructor at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, and colleagues found that RANK expression correlated with an increased risk of relapse. Specifically, if the patients were divided between those whose primary tumors had high RANK expression (cut-off of 63 percent or greater positive cells) and those whose tumors had low expression, there was a statistically significant difference in relapse-free survival.

The observation was validated in a second, independent cohort of 425 women from an MD Anderson Cancer Center database of women with early breast cancer who had undergone neoadjuvant chemotherapy. In that database, the difference between high and low expressors was even more significant, with a cutoff of 61 percent cell positivity.

The investigators also found that, on average, RANK expression was significantly continued on page 24

It may therefore be appropriate to consider the large protection against breast cancer recurrence if life-threatening consequences, as they did in B-31, remain low in long-term follow-up, she said. “There is a lot of caution in this area because the first principle of medicine is to do no harm, but there is no doubt that the protection provided by trastuzumab against recurrence is substantial.”

And while any cardiotoxicity raises concern, the low risk of sustained clinically relevant cardiac dysfunction seen so far in follow-up of patients on trastuzumab must be understood in the context that “when a distant recurrence occurs, breast cancer is no longer considered curable. Therefore, for most otherwise healthy women with HER2-positive early-stage breast cancer, the expected benefits typically far outweigh the cardiotoxicity risk when trastuzumab-based therapy is being considered.”

Comments from Martine Piccart-Gebhart

The support for offering anthracyclines plus an adjuvant therapy that includes trastuzumab to more women at risk of relapse appears to be gaining momentum. Martine Piccart-Gebhart, MD, PhD, Professor of Oncology at the Université Libre de Bruxelles and Director of the Medicine Department at Institut Jules Bordet, in Brussels, was a coauthor of an editorial earlier this year that preceded the release of the B-31 results but made this same point (“Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines?” Barstein et al. JCO 2012;30:2179-2182).

Summarizing the main message in an interview for this article, she said, “We still believe anthracyclines should not be abandoned too soon for patients with HER2-positive breast cancer at moderate or high risk of relapse.” She characterized the B-31 data, which support this approach, as “reassuring, given the large reversibility of [the cardiovascular] events over time.”

However, she also underlined the importance of better objective tools to identify those who should or should not be considered candidates for trastuzumab. There is now a collaborative initiative undertaken among several trastuzumab trials, including herself, she said, “to validate—or possibly refine—the cardiac score developed by the NSABP B-31 group.”

Women whose primary breast tumors express higher levels of RANK may be at higher risk of relapse and bone metastases, compared with women whose tumors express less of the protein.

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CARDIOTOXICITY

continued from page 22

There are, however, significant limitations. Mayer noted, even if the Cardiac Risk Score developed with the B-31 data is confined to those patients meeting the trial’s eligibility criteria. Still, she commended the investigators for attempting to develop predictors and suggested that further work in this area may lead to reliable and personalized risk stratification.

Targeting the Correct Population

Romond acknowledged the limitations of the scoring system, but said that the B-31 data do suggest that there is a population of patients with HER2-positive breast cancer who could benefit significantly from trastuzumab with a low risk of cardiac toxicity.

“The assessment of the best approach for an individual patient should weigh the risk from the disease, the efficacy of the therapy, and the risk from the therapy, all in the context of that patient’s health apart from cancer,” she said.

And although there is as yet no definitive method for assessing the risk of a cardiac event, the B-31 data do suggest that specific characteristics can be identified that confer a very low risk and high likelihood of deriving a favorable risk-to-benefit from treatment with an anthracycline-based regimen that includes trastuzumab—and not least importantly, there does not appear to be a substantial late risk for a cardiac event once therapy is discontinued.

Other Models

Also asked for her opinion for this article, Heather McArthur, MD, MPH, a medical oncologist who specializes in breast cancer at Memorial Sloan-Kettering Cancer Center, noted that this is, of course, not the first effort to create a model with which to predict the risk of cardiotoxicity. And while such models are helpful for clinicians attempting to balance the risk of the proposed treatment recommendation against the expected benefit, “I think that many physicians are already taking these risk factors into consideration,” she said.

One of the most pressing problems in this area, she noted, is the inconsistency of definitions for cardiac events. For example, in B-31, there was one case of the most feared complication, death by congestive heart failure, in each arm.

Although the event rate, which included a much broader definition of cardiotoxicity, was four percent, trastuzumab has been associated with breast cancer recurrence reductions of approximately 50 percent in randomized trials.

In a retrospective review that she led at her own institution, this type of relative risk reduction was observed even among low-risk HER2-positive patients with node-negative malignancies, she noted.

It may therefore be appropriate to consider the large protection against breast cancer recurrence if life-threatening consequences, as they did in B-31, remain low in long-term follow-up, she said. “There is a lot of caution in this area because the first principle of medicine is to do no harm, but there is no doubt that the protection provided by trastuzumab against recurrence is substantial.”

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