Cardiac side-effects of trastuzumab: lessons learned from targeting cancer pathways

Debu Tripathy

A recent study has found that symptomatic cardiac toxicity may be a little higher in actual practice than in reports from the clinical trial of trastuzumab, and this finding needs to be incorporated into decision making, especially for lower-risk cases.

Unexpected toxicity from agents that target cancer-related pathways will become a more familiar theme as we are ushered into the era when these agents outnumber standard chemotherapeutic drugs. The signaling networks of carcinogenesis, growth, development and metabolism are interrelated and complex, with clinical effects that are difficult to predict.

It has long been recognised that deregulation of developmental genes can be carcinogenic as a result of the inappropriate recapitulation of the phenotype of embryonic cell migration and invasion of tissue boundaries. During the latter phases of the pivotal randomised trials of the HER2-oncogene-directed antibody trastuzumab it became apparent that cardiomyopathy was an uncommon treatment-related complication, which was more pronounced in those receiving concurrent cardiotoxic anthracycline therapy.[1]

At about the same time, findings of the HER2 knockout mouse were reported, showing impairment of the development of cardiac trabeculae and cranial neural-crest-derived sensory ganglia.[2] More recent studies have shown that cardiac myocyte-targeted HER2 gene knockout in adult mice leads to impaired cardiac remodeling in response to stress.[3]

It is, therefore, expected that trastuzumab could have some effect on cardiac function, just as EGFR-modulating drugs like erlotinib, cetuximab and lapatinib affect EGFR-expressing tissue including the gastrointestinal tract and skin. The critical issue of balancing benefits and harms, which applies in any medical decision, requires a full knowledge of the long-term risk and the role of specific host variables in the manifestations of this risk.

In metastatic disease, morbidity and mortality due to cancer far outweigh the cardiac risks of trastuzumab and also limit observations of long-term cardiac effects. Follow-up from the much larger adjuvant trials is limited, with clinical cardiomyopathy seen in 2–4% of patients, who usually recover over time, yet it is not clear whether long-term effects from a full year of therapy may emerge even decades later.

The report by Guarneri and colleagues (see opposite) provides some unique insights on long-term therapy, with a median exposure time of nearly two years and a follow-up time of almost three years in 173 patients. The overall cardiac event (CE) rate of 28% was higher and late events more frequent than previously reported in the pivotal randomised trial,[4] perhaps reflecting a more 'real-life' patient population than that seen in clinical trials, where exclusion criteria are more stringent.

Recovery was seen in 11 of the 15 patients who developed symptomatic heart failure and in 30 of 34 asymptomatic patients. However, the role of therapy for cardiomyopathy, while clinically indicated, is unclear since resolution can also be seen without therapy.

Endomyocardial biopsy of three patients with CEs did not show the

Debu Tripathy is Professor of Internal Medicine and Director of the Komen/University of Texas Southwestern Breast Cancer Research Program, University of Texas Southwestern Medical Center, Dallas, Texas, USA. *The author has declared associations with Genentech*
This article was first published in *Nature Clinical Practice Oncology* 2007 vol. 4 no. 4, and is reproduced with permission
www.nature.com/clinicalpractice, doi:10.1038/ncponc0768, ©2007 Nature Publishing Group

usual anthracycline-associated loss of contractile elements, but ultrastructural examination did reveal pleomorphic mitochondria and myocardial cell hypertrophy typical of reversible insults, suggesting distinct mechanisms.

While these results add to our knowledge of longer-term CEs and confirm the short-term reversibility in most cases, they still do not address the crucial risk/benefit question for adjuvant therapy, for which the risk of mortality from non-cancer events is higher than that from breast cancer. Unfortunately, there is no substitute for careful follow-up from randomised trials with consistent criteria for CEs, which are notoriously difficult to adjudicate and differentiate from pulmonary or other non-cardiac etiologies. We should incorporate this contingency into risk/benefit calculations for lower-risk HER2+ early-stage cases and ensure that long-term follow-up from clinical trials continues with rigorous monitoring and frequent updates.

References

1. A Seidman et al. (2002) Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 20:1215–1221
2. KF Lee et al. (1995) Requirement for neuregulin receptor erbB2 in neural and cardiac development. *Nature* 378:394–398
3. SA Crone et al. (2002) ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med* 8:459–465
4. D Tripathy et al. (2004) Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol* 15:1063–1070

Synopsis

V Guarneri, DJ Lenihan, V Valero et al. (2006) **Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience.** *J Clin Oncol 24:4107–4115*

Background. Trastuzumab therapy is generally well tolerated but its use, especially in conjunction with anthracyclines, has led to an unexpectedly high incidence of cardiac toxicity. Trastuzumab induces cardiac damage that is dose-dependent.

Objective. To determine the cardiac safety of trastuzumab in patients with HER2-overexpressing metastatic breast cancer.

Design and intervention. Patients with HER2-overexpressing metastatic breast cancer who had received trastuzumab at the MD Anderson Cancer Center in Houston, Texas, for 1 year or longer were identified through a database search of patients treated up until December 2003. Left ventricular ejection fraction (LVEF) was assessed either by echocardiography or multiple-gated acquisition scanning. Cardiac events (CEs) were defined as a decrease in LVEF of 20 percentage points compared with baseline or below the normal level (50%), or symptoms or signs of congestive heart failure (CHF). Cardiac toxicity was graded by version 3.0 of the National Cancer Institute Common Toxicity Criteria for Adverse Events. A cardiologist assessed patients who had cardiac symptoms or a decrease in their LVEF. Patients with an asymptomatic decrease in LVEF below 40% or CHF did not continue to receive trastuzumab. Other cases were individually considered for trastuzumab treatment, as were patients who recovered their cardiac function after ceasing trastuzumab treatment.

Outcome measure. The primary end point of the study was occurrence of a CE.

Results. Among 173 patients (median age 50 years; range 26–79 years) receiving trastuzumab for a median cumulative period of 21.3 months (range 11.6–77.6 months), a CE occurred in 49 patients (28%). Follow-up was 11.8–79 months (median 33.6 months). In total, 3 patients (1.7%) had a decrease in LVEF of 20 percentage points, 27 patients (15.6%) developed grade 2 cardiac toxicity and 19 patients (10.9%) developed grade 3 cardiac toxicity. Only 15 of the 49 patients diagnosed with cardiac toxicity had symptoms at diagnosis, and of this group 14 discontinued trastuzumab and 11 responded to specific cardiac therapy. Three patients did not recover while receiving specific cardiac therapy, one of whom died of CHF. One patient recovered quickly on specific cardiac therapy and trastuzumab was not discontinued. Among the patients who had asymptomatic cardiac toxicity, 17 patients discontinued trastuzumab and complete recovery was documented in 15 of these patients; 2 patients did not receive additional assessment of LVEF. Complete recovery was also seen in 15/17 asymptomatic patients in whom trastuzumab was continued; additional LVEF assessment was not available for the other 2 patients. In the 26 patients re-treated with trastuzumab, 10 patients had CEs. Baseline LVEF was associated with CE (hazard ratio 0.94; P=0.01). The risk of a CE occurring in patients receiving concomitant taxanes was increased early in the follow-up period but decreased later.

Conclusion. Cardiotoxicity of long-term trastuzumab-based therapy represents an acceptable risk in patients with HER2-overexpressing metastatic breast cancer, and this toxicity is reversible in most patients.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice.*