Fifteen Years of Anti-HER2 Therapy

By Nancy E. Davidson, MD [5]

Last month brought the accelerated approval by the US Food and Drug Administration (FDA) of a fourth agent targeting the human epidermal growth factor receptor 2 (HER2) oncogene product: TDM-1 (Kadcyla), a conjugate of trastuzumab and a cytotoxic, emtansine.

The stage was set by the near-simultaneous reports in 1985 from three different labs about the identification of a gene variously called HER2, v-erbB2, or EGFR2. Ultimately, it became clear that the HER2 protein is a member of a family of four transmembrane tyrosine kinase receptors that interact with a variety of ligands. Within a couple of years, the pivotal observation that the HER2 protein is overexpressed in a percentage of breast cancers, generally because of gene amplification, led to a series of functional studies, culminating in the hypothesis that blockade of the signaling pathway would inhibit breast cancer cell growth. From this line of study ultimately came the agent trastuzumab (Herceptin); this saga is nicely chronicled in a book by science reporter Robert Bazell, HER-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer.

The ability of a combination of trastuzumab and chemotherapy to extend survival in patients with advanced breast cancer that overexpressed HER2 led to trastuzumab’s approval by the FDA in 1998. That decision, combined with an acceptable toxicity profile, led to the rapid launch of four international trials of trastuzumab in the adjuvant therapy setting, trials whose results were stunningly similar both in initial reports in 2005 and in more mature reports published in the last year or two. At present, 1 year of trastuzumab appears to be the standard anti-HER2 targeted therapy for women with HER2-overexpressing invasive breast cancer.

As clinical use and investigation of trastuzumab progressed, attention turned to other ways to intervene in the HER2 signaling pathway. Mechanism-based studies led to the development of a small-molecular tyrosine kinase inhibitor, lapatinib (Tykerb); a monoclonal antibody that inhibits HER dimerization, pertuzumab (Perjeta); and a conjugate of trastuzumab with a cytotoxic as a form of targeted delivery, TDM-1. Progress was greatly accelerated by our enhanced understanding of the HER signaling pathway and by our ability to enrich study populations for individuals with HER2-overexpressing breast cancer (with such enrichment based on the assumption that benefit would be limited to that molecular subtype). As a result, much attention has been focused on accurate and reproducible measurement of HER2 status, an initiative championed by the American Society of Clinical Oncology and the College of American Pathologists. In addition, the use of preoperative therapy clinical trial designs has expedited the clinical development process.

So what is left to do? More than we might wish. First, some women with HER2-positive tumors demonstrate de novo or acquired resistance to anti-HER2 therapy, and our knowledge of mechanisms of HER2 resistance is lacking. A corollary is that we lack clinically useful markers of response or resistance beyond HER2. Second, we have much to do to optimize our therapy by addressing questions of sequence, duration, and combinations of anti-HER2 targeted agents. Third, the utility of stand-alone anti-HER2 therapy or combination therapy with other biologics remains underexplored. Indeed, a stretch goal would be to identify women with HER2-overexpressing breast cancer who would be candidates for biologic therapy alone, unaccompanied by chemotherapy.

Finally, tantalizing data from the pivotal adjuvant trials suggest that benefit from anti-HER2-directed therapy may not be restricted to those women whose tumors overexpress HER2. Indeed, a current phase III trial is evaluating the hypothesis that trastuzumab may improve outcomes in women receiving adjuvant chemotherapy for invasive cancers that have 1 or 2+ HER2 expression.
Although our work is incomplete, progress against HER2-positive breast cancer is palpable. Anti-HER2 therapy joins endocrine therapy as a cornerstone of targeted therapy in breast cancer and a “poster child” for precision or personalized cancer care. In addition, it may create traction for the treatment of other types of cancer that also overexpress HER2, such as rare gastric cancers or lung adenocarcinomas. Finally, it stands as a paradigm for drug development—because of the success of patient selection through the pairing of a diagnostic test and a targeted therapy, and the use of novel preoperative trial designs in addition to the classic sequence of testing in metastatic disease followed by adjuvant trials.

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