Current Challenges in Human Epidermal Growth Factor Receptor-2-positive Breast Cancer – Treating Disease Progression

a report by

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DOI: 10.17925/EOH.2007.0.1.19

Human epidermal growth factor receptor-2 (HER-2) is a transmembrane tyrosine kinase receptor that belongs to the epidermal growth factor receptor (EGFR) family, and is overexpressed in 25–30% of human breast cancers. HER-2 overexpression/amplification is associated with aggressive disease, short disease-free intervals and reduced survival.[1,2] In these patients with poor prognosis, the HER-2 protein is an important therapeutic target and its overexpression is found both in the primary and in metastatic sites.[3]

Trastuzumab (Herceptin®, Genentech Inc., San Francisco, California) is a recombinant humanised monoclonal antibody directed against the extracellular domain of the HER-2 protein. There are several mechanisms by which trastuzumab exerts its action, including:

- induction of receptor downregulation/degradation;[4]
- prevention of HER-2 ectodomain cleavage;[5]
- inhibition of HER-2 kinase signal transduction via antibody-dependent cell-mediated cytotoxicity (ADCC);[6] and
- inhibition of angiogenesis.[7]

As a single agent in the metastatic setting, overall response rates (complete plus partial responses) ranging from 15 to 30% have been reported.[8] In combination with chemotherapy – including taxanes and vinorelbine – response rates can range from 50 to 80%.[9,10] These positive results led to trastuzumab approval by the US Food and Drug Administration (FDA) in 1998 for the treatment of metastatic breast cancer in combination with chemotherapy.

In the EU, trastuzumab was approved on 28 August 2000 both as monotherapy for patients who have undergone at least two chemotherapy regimens and in combination with a taxane for those not previously treated for their metastatic disease.

Encouraged by the experience in the metastatic setting, four major international studies of adjuvant trastuzumab with enrolment of over 13,000 women were launched in 2000–2001: Herceptin Adjuvant Trial (HERA)[11] and the combined North American trials National Surgical Adjuvant Breast and Bowel Project (NSABP) B31, North Central Cancer Treatment Group (NCCTG) N9831[12] and Breast Cancer International Research Group (BCIRG) 006.[13] In 2005, the initial results of these four trials, alongside a smaller Finnish trial, FinHer,[14] were released; these results were not only astonishing, but also highly consistent.

Despite differences in patient population and trial design – including chemotherapy regimen, the timing of trastuzumab initiation and the schedule and duration of trastuzumab administration – clinical benefit was observed across all trials, with 39–52% reduction in the recurrence rate and a 30% reduction in mortality. This degree of benefit in early breast cancer is the largest reported since the introduction of tamoxifen in hormone-receptor-positive disease.

Without much doubt, trastuzumab has had unfettered success in the metastatic and adjuvant setting; however, the reality is that not all patients will have an initial response, and in those who do, trastuzumab resistance often develops within one year of treatment initiation.[15] This is because tumorigenesis is a complex multi-step process, and in breast cancer therapeutic success will, indeed, need to rely on the targeting of multiple rather than single targets.

Many of the mechanisms of resistance to trastuzumab are not well characterised, but there are several hypotheses:

- altered receptor–antibody interaction with masking of HER-2 by a membrane-associated glycoprotein mucin-4 (MUC4);[16]
- increased signalling from other HER receptors;
- phosphatase and tensin homologue (PTEN) inactivation or loss, resulting in increased Akt activity;[17]
- reduced p27kip1;[18]
- increased insulin-like growth factor receptor signalling;[19] and
- an inability of monoclonal antibodies to bind and inhibit p95 HER-2 (truncated forms of HER-2 without extracellular domains).[20]

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Beyond trastuzumab's initial success, effort is now being put into the development of novel HER-2-targeting agents, including other monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and vaccines. These agents are being evaluated in the metastatic setting in combination with trastuzumab, in combination with other cytotoxic chemotherapy or as single agents as a strategy to overcome trastuzumab resistance.

> Lapatinib is a small-molecule tyrosine kinase inhibitor that is capable of dual-receptor inhibition of both epidermal growth factor receptor and human epidermal growth factor receptor-2.

These novel drugs have variable but interesting properties, including:

- dual inhibition against EGFR and HER-2, such as lapatinib, pertuzumab and HKI-272;
- antiangiogenesis, such as bevacizumab or pazopanib;
- anti-mammalian target of rapamycin (mTOR) action, such as temsirolimus; and
- anti-Hsp90 action, such as 17-AAG.

However, having a multitude of new molecularly targeted drugs in our anticancer armamentarium is simply not good enough. The clinical dilemma, in fact, is in the choice of which agents to use next, whether it is with recurrence after adjuvant trastuzumab or with emerging resistance with trastuzumab use in the metastatic setting.

Many lessons have already been learned from the various clinical trials designed to find an answer to this problem. In exploring the potential for using an altogether different molecularly targeted therapy, lapatinib probably deserves a special mention. Lapatinib is a small-molecule TKI that is capable of dual-receptor inhibition of both EGFR and HER-2. In phase I/II studies as a single agent, lapatinib has resulted in objective responses between 4.3 and 7.8% in HER-2-positive patients who had progressed on multiple trastuzumab-containing regimens,[21] with a substantial number having stable disease at four months (34–41%) and six months (18–21%).

In the EGF10151 study,[22] capecitabine, with or without lapatinib, was given to 321 patients with HER-2-positive, locally advanced or metastatic breast cancer refractory to trastuzumab and previously treated with anthracyclines and taxanes. In the initial published results of this phase III study, there was significant improvement in the median time to progression (TTP) for patients receiving lapatinib and capecitabine compared with patients treated with capecitabine alone (8.4 months versus 4.4 months, respectively; p=0.00032). Furthermore, the incidence of central nervous system (CNS) relapse was lower in the lapatinib plus capecitabine group (n=4; 2%) than in the capecitabine group (n=11; 7%). The recent update at the American Society of Clinical Oncology (ASCO) 2007[23] confirmed this benefit in TTP (27 weeks versus 19 weeks) with a hazard ratio (HR) of 0.57 (95% confidence interval (CI) 0.43–0.77; p=0.00013) as well as the benefit in CNS progression (2% versus 11%; p=0.0445). This study has been pivotal in demonstrating that the HER-2 receptor remains a viable target even after initial trastuzumab failure, and that lapatinib has an effect on the development of CNS metastases.

Based on these results, on 13 March 2007 the FDA granted approval to lapatinib tablets (Tykerb/Tyverb, GlaxoSmithKline) for use in combination with capecitabine for metastatic, trastuzumab-refractory breast cancer patients with prior anthracycline and taxane treatment. The combination was also approved in Switzerland on 23 May 2007. Additionally, following success in the metastatic setting, lapatinib is now being evaluated in two adjuvant trials. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial is a four-arm, randomised, adjuvant study comparing one-year therapy of lapatinib, trastuzumab, its combination, or an interesting sequence of 12 weeks of trastuzumab followed by a six-week wash-out period and then 34 weeks of lapatinib. It is anticipated that the ALTTO study will accrue 8,000 patients with HER-2 positive early breast cancer worldwide.[24] On the other hand, Tykerb Evaluation After CHemotherapy (TEACH) is a phase III randomised, multicentre trial evaluating the effectiveness of 12 months of lapatinib given as either immediate or delayed therapy in HER-2-positive early breast cancer. The trial will look at the primary objective of disease-free survival, and will enrol approximately 3,000 patients.

Other studies have shown that using different combinations of molecularly targeted agents with the continuation of trastuzumab may be an important therapeutic strategy, but only if rationally applied. The phase II Eastern Co-operative Oncology Group (ECOG) 1100 study[25] was indeed disappointing in its evaluation of weekly trastuzumab and gefitinib – an EGFR TKI – in 36 HER-2-positive metastatic breast cancer patients, resulting in only one complete and one partial response, and a median time to progression of only 2.9 months (95% CI 2.5–4.0). This combination appeared antagonistic perhaps because HER-3 was not blocked and a switch to a survival pathway may have occurred.

> Lapatinib has an effect on the development of central nervous system metastases.

Other studies, nevertheless, have been more promising. Storniolo et al.[26] found response rates of 29% in combining trastuzumab and lapatinib in a dose-escalation study, and Pegram et al.,[27] in a phase I/II study, found an overall response rate of 54.1% in 37 metastatic HER-2-positive patients by combining trastuzumab with bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody.

Other current exciting studies include HKI-272, a highly selective irreversible inhibitor of HER-2 and EGFR, which is capable of blocking downstream signal transduction of mitogen-activated protein kinase (MAPK) and Akt phosphorylation, downregulating cyclin D1 levels and

inducing p27.[28] Pertuzumab (Omnitarg®) is a fully recombinant humanised monoclonal antibody that targets a different epitope of HER-2 and therefore makes it an attractive therapeutic option for trastuzumab-resistant patients.[29] An ansamycin antibiotic inhibitor of the heat-shock protein, HSP-90 (17-AAG) can interfere with multiple intracellular signal transduction pathways involving the Src family, Akt, bcr-abl, cyclin-dependent kinases and other transcription factors.[30]

An interesting therapeutic strategy may also be in blocking the oestrogen receptor and HER-2 pathways because of the cross-talk that occurs between signal transduction and endocrine pathways. In the TAnDEM study,[31] the addition of trastuzumab to anastrozole significantly improved clinical outcomes for HER-2 and hormone receptor (HR)-positive metastatic breast cancer patients, with a doubling of progression-free survival (4.8 months versus 2.4 months; p=0.0016) and a tripling of the overall response rate (20.3% versus 6.8%; p=0.018), and more than 15% of patients receiving both did not progress for at least two years, with the advantage of delaying chemotherapy.

In summary, the experience with trastuzumab thus far can only be described as a successful one, although – with the increasing use of trastuzumab in the adjuvant setting – the speculation is that trastuzumab resistance will be encountered more frequently in the future. Indeed, it is time to move forwards from this initial success and endeavour to refine therapeutic strategies for the use of novel molecularly targeted agents for trastuzumab-resistant patients; these should not only be clinically beneficial and scientifically sound, but also economically sustainable.

The optimal duration of trastuzumab treatment is still unknown and the question of whether to continue with or cease trastuzumab altogether at the point of disease progression remains empirically based. Furthermore, if trastuzumab is to continue, would a change in the companion chemotherapeutic agent be sufficient or must another molecularly targeted agent be added?

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Translational oncology will hold the key to many of these unresolved issues by improving the understanding of tumour biology. As new molecular targets are increasingly identified and corresponding therapeutics are developed, the parallel development of translational tools that can help identify optimal candidates for each of the therapeutic approaches should also occur. Furthermore, it is only with well designed trials based on solid biological and molecular evaluations that the initial success with trastuzumab can lead to other successes in the exciting era of molecularly targeted therapy. ■

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