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HER2—a good addiction

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Abstract

Recent neoadjuvant studies have examined the effects of adding single or dual agents targeting HER2 to chemotherapy, finding unanimously that dual HER2 targeting markedly improves pathologic response. These findings have significant implications for future trial designs, particularly if the impact on pathologic response is accompanied by improved disease-free survival or overall survival.

Oncogene addiction is defined as a cell becoming so reliant on one signaling pathway for growth and survival that blockade of that pathway, and that pathway alone, is lethal for such a cell.[1] This is uncommon, but therapeutically exploitable because it confers exquisite and persistent sensitivity to drugs targeting that oncogene. Examples of addicted tumors include EGFR-activated lung cancers, gastro-intestinal stromal tumors with mutations in *KIT,* and HER2-positive breast cancers. The hypothesis of *HER2* gene addiction in breast cancer is supported by several recent neoadjuvant studies, including GeparQuinto,[2] NeoALTTO,[3] CHER-LOB,[4] and NeoSphere.[5] These studies all suggested that optimal treatment of HER2-positive breast cancer should involve multiple HER2-targeted drugs in combination.

Before the publication of these neoadjuvant studies, clinical support for the concept of oncogene addiction in HER2-positive breast cancer came from studies in metastatic disease.[6] Typically, clinicians who chose to treat patients with cytotoxic agents changed to a non cross-resistant agent upon progression of the disease. The treatment paradigm with HER2-targeted therapy is different. For example, continued HER2 targeting works even after disease progression. This was first demonstrated by studies showing that after disease progression on regimens containing the anti-HER2 monoclonal antibody trastuzumab, treatment regimens containing the dual HER1-HER2 tyrosine kinase inhibitor lapatinib improved progression-free survival (PFS).[6] To be clear, this means that despite tumor progression while receiving one anti-HER2 drug, patients benefited from treatment with a different, but still HER2-targeted, drug. Nonetheless, although lapatinib and trastuzumab both target HER2, they do so in markedly different ways so perhaps it is the change in drug mechanism of action that permits different effects when targeting the same protein in the same patient. More compelling evidence comes from a small study that demonstrated that

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Competing interests

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patients with disease progression following a trastuzumab-based regimen had improved PFS if the trastuzumab regimen was continued after changing chemotherapy.[7] Supporting the addiction paradigm further, resistance can be circumvented by adding new HER2-targeted drugs in addition to the HER2-targeted drugs to which the cancer has become resistant. This strategy works better than the more-conventional approach of simply changing drugs. The most elegant illustration of the benefit of this approach comes from a randomized study in which metastatic HER2-positive breast cancer in patients resistant to trastuzumab had a worse response if the drug was changed to lapatinib than if lapatinib was added to trastuzumab.[8] This study was notable in that it asked a pure biologic question without the confounding issues of chemotherapy synergy, and leads one to wonder if initial complete HER2 blockade would improve outcome over sequentially adding more HER2-targeted drugs. That question was addressed by the randomized phase III study CLEOPATRA,[9] in which dual targeting of HER2 with both trastuzumab and pertuzumab—an antibody that inhibits HER2 dimerization—combined with a paclitaxel chemotherapy backbone improved PFS by over 6 months compared with the control arm of paclitaxel plus trastuzumab alone.

Four published trials using different HER2-targeted drugs in patients with early stage breast cancer have now added to the mounting evidence that combined and ongoing HER2 targeting improves outcome in metastatic HER2-positive breast cancer. All four trials took advantage of the neoadjuvant paradigm to study optimal HER2 targeting added to chemotherapy in early stage breast cancer, and the findings from all four studies were remarkably concordant. In the GeparQuinto study,[2] 620 patients with high-risk, HER2-positive breast cancer were randomly assigned to receive chemotherapy (epirubicin and cyclophosphamide [EC] followed by docetaxel [D]) with either trastuzumab (EC–DH) or lapatinib (EC–DL) for a total of 24 weeks as preoperative therapy. In this phase III trial, the EC–DH arm was statistically superior to EC–DL in terms of pathologic complete response (Table 1; pCR, defined here as absence of invasive cancer in the breast and axillary lymph nodes), and was better tolerated.[2]

Two of the other studies, NeoALTTO and NeoSphere, addressed directly the question of whether initial dual targeting is better than single targeting. The phase III NeoALTTO study[3] randomly assigned 455 patients to receive paclitaxel (T) with trastuzumab (TH), with lapatinib (TL), or with both HER2-targeting agents (THL). As predicted by the results from the metastatic setting,[9] dual HER2-targeting with THL outperformed both single HER2-targeting arms; the lowest pCR rate was observed with TL. The small non-comparative CHER-LOB study similarly found twofold higher pCR rates with the combination of chemotherapy and TL than with the combination of chemotherapy with either of the two HER2-targeted drugs (T or L) as a single agent.[4] The randomized phase II study NeoSphere[5] examined a different HER2-targeted agent, pertuzumab (P), but arrived at similar conclusions. One arm assessed both anti-HER2 agents, trastuzumab and pertuzumab, alone without chemotherapy. Although this arm had the lowest pCR rate, it is of interest because of the avoidance of any cytotoxic agent. The other three arms included docetaxel. In those arms, as in the NeoALTTO study, the combination of chemotherapy plus dual HER2-targeting was superior to chemotherapy plus a single HER2-targeted drug, and treatment with pertuzumab alone was inferior to, and was more toxic than, trastuzumab.[5]

Neoadjuvant trials from the US Cooperative Group will soon add to the available data. Both NSABP B-41 (NCT00486668) and CALGB 40601 (NCT00770809) examined trastuzumab or the combination of trastuzumab plus lapatinib added to chemotherapy. In CALGB 40601, only paclitaxel was given with HER2-targeting agents, and the trial permitted discretionary administration of an additional adjuvant anthracycline, a first step towards tailoring therapy according to response.

What can we learn from the neoadjuvant experience in these studies? First, none of the newer HER2-targeted agents was better than trastuzumab when added to chemotherapy. This is interesting but far less impressive than the finding that dual HER2-targeting was better than any single agent. Clinically relevant end points of disease-free survival and overall survival are not yet mature, but in previous studies in HER2-positive disease, pCR predicted improvements in these end points. If dual HER2-targeting becomes the norm, this has significant implications for future clinical trials, standard therapy and cost consideration. Do all HER2-positive tumors need multiple drugs targeting HER2? Certainly not; pCR rates in response to single HER2 targeting added to chemotherapy range from 20–30% (Table 1), and arguably these patients need nothing more. How will we incorporate even newer HER2-targeted drugs such as trastuzumab-DM1? How will we determine which patients need which drugs and how many? Clearly, well-performed correlative studies are the only way we will understand the complex biology enough to tailor therapy, and the neoadjuvant setting facilitates these studies. All of these neoadjuvant trials have included tissue-based studies, and NeoALTTO and CALGB 40601 required both fresh and fixed tissue for predictive biomarker discovery.

“Do all HER2-positive tumors need multiple drugs targeting HER2? Certainly not…”

The strategy for treating HER2-positive breast cancer is becoming clearer. In both the metastatic and early stage breast cancer settings, targeting HER2 itself is the linchpin of therapy; it is reasonable to assume that better and more comprehensive HER2-targeting will result in lives saved. In addition, because HER2 and its related pathways are central to this subset of breast cancers, correlative science studies to identify predictive factors can remain focused on the biology of this pathway. This issue of identification of predictive factors is the most important one facing us today; we cannot, and should not, treat every patient with every drug in the arsenal. Our challenge is to become more selective in our use and combination of these drugs. Given the number of effective drugs and the therapeutic consequence of HER2 addiction, we may solve the problem of personalized therapy first in HER2-positive disease.

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Practice point

The results of these studies suggest that dual HER2-targeting should be used in the metastatic setting and should be considered as neoadjuvant therapy for locally advanced HER2-positive breast cancer.

Table 1 |

pCR rates* in HER2-targeted trials

Study	*n*	Regimen	pCR (%)
GeparQuinto[2]	620	EC–T + H	45
		EC–T + L	30
NeoSphere[5]	417	D + H	22
		D + P	18
		D + HP	39
		HP	11
NeoALTTO[3]	455	T + H	28
		T + L	20
		T + HL	47
CHER-LOB[4]	121	T–FEC + H	25
		T–FEC + L	26
		T–FEC + HL	47

*Absence of invasive tumor in the breast and axilla.

Abbreviations: C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; H, trastuzumab; L, lapatinib; P, pertuzumab; pCR, pathologic complete response; T, paclitaxel.