

Individualization of neoadjuvant therapy for breast cancer according to molecular tumor characteristics

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The development of therapies directed at specific molecular abnormalities within cancer cells is currently an important goal of investigational oncology. The relatively recent development of hormone receptors and human epidermal growth factor receptor 2 (HER2) as validated targets of therapy has moved us rapidly towards this goal. The dramatic disease-free-survival benefits associated with adjuvant trastuzumab in the treatment of patients with HER2-amplified breast cancer validate this approach as a rational and potentially very rewarding strategy.¹

Neoadjuvant systemic therapy is standard treatment for patients with locally advanced and large operable breast cancer who desire breast-conserving surgery, and is also being assessed in earlier-stage disease.² Although randomized studies have not shown a survival advantage for patients with operable breast cancer treated with neoadjuvant vs postoperative chemotherapy, patients who achieve a primary tumor pathologic complete response (pCR) have a significantly better outcome than do those with residual disease.³

Breast cancer is a molecularly heterogeneous disease. Currently, clinicopathologic criteria guide adjuvant chemotherapy decisions, but this approach does not accurately define tumor biology. Tumors of the same grade and stage often behave very differently, and the molecular mechanisms underlying metastasis and chemoresponsiveness are not well understood. Traditionally, breast cancer has been classified as hormone receptor (HR)-positive or HR-negative. Recently, transcriptional profiling has revealed six molecular subtypes, which correlate well with the traditionally recognized subgroups (see Supplementary Table 1 online).⁴ These subtypes each have different molecular, prognostic, and predictive features, but our understanding of these differences is still limited.

Cytotoxic chemotherapy is conventionally regarded as a nontargeted approach to treatment and is utilized in all breast carcinoma subtypes, guided by factors including tumor grade and stage.

The relative benefits of cytotoxic chemotherapy can be predicted by HR status and grade. The presence of HRs and *HER2* amplification, which define certain breast cancer subtypes identified by transcriptional profiling, now guide the use of targeted therapies, which benefit only breast cancer patients with tumors that exhibit the target of that particular therapy.^{1,5} The addition of trastuzumab to neoadjuvant chemotherapy increased the pCR rate from 26% to 65% in a small phase III trial in patients with *HER2*-amplified breast cancer.⁶ These benefits were subsequently confirmed by large adjuvant randomized trials.¹ Interestingly, pCR rates were similar in patients with *HER2*-amplified tumors, regardless of estrogen receptor (ER) status. Neoadjuvant endocrine therapy has significant activity in patients with HR-positive breast cancer, with objective response rates of up to 60%.⁷ Patients are likely to derive more benefit from endocrine therapy when the breast cancer is positive for both ERs and progesterone receptors (PgR).⁸

Neoadjuvant trastuzumab-based cytotoxic chemotherapy is currently accepted as standard of care in patients with locally advanced and large operable *HER2*-amplified breast cancer, and should be employed in any patient with *HER2*-amplified breast cancer in whom primary systemic therapy is being considered. Neoadjuvant endocrine therapy is currently not recommended as standard care in patients with HR-positive breast cancer, because of low pCR rates, although this evidence is generally based on only 3–4 months' treatment, and neoadjuvant chemotherapy also produces low pCR rates in patients with breast cancer positive for ER and/or PgR.

Only some patients with *HER2*-amplified breast cancer benefit from the addition of trastuzumab to chemotherapy; the pCR rate was 65% in the study of Buzdar *et al.*, and the relative risk reduction associated with the addition of trastuzumab to adjuvant chemotherapy was ~50%.^{1,6} Similarly, in patients with HR-positive breast cancer, the response rates to neoadjuvant endocrine therapy are only as high as 60%, and the relative risk reductions associated with endocrine therapy in

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the adjuvant setting are approximately 50–60%.⁵ Thus, a significant proportion of tumors with the required molecular target are, or become, resistant to the targeted therapy. In addition, patients with so-called ‘triple receptor-negative’ breast cancer (i.e. negative for HRs and HER2) currently lack a validated target that can be exploited. There is preliminary evidence of epidermal growth factor receptor (*EGFR*) overexpression in this group of tumors; in addition, most *BRCA1*-mutated tumors fall into the ‘triple negative’ category, and many of these carry *p53* mutations.

Neoadjuvant therapy is an ideal setting in which to explore the activity of new targeted therapies. Although most large neoadjuvant studies have used primary tumor pCR as an endpoint, pCR of cytologically-proven metastatic disease in axillary nodes might be a better surrogate endpoint.⁹ Based on very low pCR rates, neoadjuvant chemotherapy might be unsuitable for patients with low grade tumors or with strongly ER-positive and PgR-positive breast cancers. We and others are utilizing transcriptional profiling to identify gene expression patterns and markers associated with therapy responsiveness. For example, the importance of tau to taxane responsiveness has emerged from such studies. As the treatment of breast cancer begins to diverge depending upon the subtype and expression (or amplification, activation, mutation, etc.) of particular proteins, the identification of further valid targets within each breast cancer subtype will likely lead to further diversification, possibly even to individualization of therapy. As mechanisms of trastuzumab and endocrine therapy resistance are explored, potential targets are identified for further study. For example, *PTEN* underexpression and insulin-like growth factor 1 receptor (IGF-1R) overexpression are potential mechanisms of trastuzumab resistance.^{10,11} With HR positivity, there is apparent crosstalk between ER and EGFR/HER2 pathways, and this has potential effects on resistance to endocrine therapies. The frequent identification of phosphatidylinositol 3-kinase pathway abnormalities in HR-positive breast tumors, such as *PI3K* mutations, *PTEN* losses, and *HER2* and *cyclin D1* amplifications, indicates that these abnormalities need to be explored for their role in endocrine therapy resistance.¹² Perhaps most urgently, we must identify rational, valid molecular therapeutic targets in patients with ‘triple receptor-negative’ breast tumors. Although there is certainly overlap, there are some known associations between genomic abnormalities and

breast cancer subtype as defined by the expression of HRs and HER2 (see Supplementary Table 1 online). Novel high-throughput technologies, including transcriptional profiling and array-based comparative genomic hybridization, might assist us in the identification of novel targets that are not only expressed and active at the protein level but also aberrant at the genomic level. Thus, the integration of genomic and proteomic approaches into the search for targets will be more fruitful than either approach alone, and will allow further individualization of breast cancer therapy.

Supplementary information is available on the *Nature Clinical Practice Oncology* website.

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Competing interests

The authors declared they have no competing interests.