Surrogate Markers for Targeted Therapy–Based Treatment Activity and Efficacy

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Predictive biomarkers capable of discriminating individuals who will benefit from a given therapy from those who will not are key to personalized medicine. New drugs are developed in patients with advanced disease, when ethical and practical shortcomings limit the collection of tumor specimens. The neoadjuvant setting offers a unique opportunity for overcoming these limitations. Tumor samples are collected at diagnosis and posttreatment surgery as part of a routine therapeutic approach. Pathological complete response has been consistently associated with long-term survival and may be useful as an intermediate endpoint in developing and evaluating predictive, as well as surrogate, biomarkers. In window-of-opportunity studies, new drugs are administered shortly before planned surgery, and the effect of the intervention can be assessed by comparing diagnostic biopsy with the surgical specimen. Until now, clinically useful and validated predictive markers for targeted therapy are rare, but appropriate investigations in neoadjuvant studies will likely change this.


Molecular heterogeneity exists even within tumors derived from the same tissue of origin, and clinical benefit associated with any drug is typically limited to a subset of patients. This aspect of cancer and cancer therapy remains the most challenging, even in the current era of “targeted therapy,” which is characterized by a move from the empiric approach of “one size fits all” to personalized therapy (1). The missing link for achieving this goal is the availability of robust and validated predictive biomarkers endowed with the discriminating power to identify those individuals who will derive benefit from a particular targeted therapy from those who will not. The model of preoperative systemic therapy is a powerful tool for studies aiming to discover and validate surrogate biomarkers.

Challenges in Development and Validation of Surrogate and Predictive Markers

A few definitions, summarized in Table 1, will help in setting a common language. The field of breast cancer therapy enjoys the availability of a high number of active targeted therapies (2), but predictive markers are scarce and limited to the expression of the estrogen and/or progesterone receptors for endocrine therapies, and HER2 amplification/overexpression for HER2-targeted drugs (3). Reasons for the gap between opportunities of targeted treatment and predictive markers are many. Relevant issues among these are: an unclear or missing scientific hypothesis, poor study design based on convenience samples with heterogeneous clinical and molecular characteristics, small sample size and underpowered studies with high false-negative and false-positive results, and poor analytical assays performance. A key element is a poor statistical design with absent or inappropriate control groups and adjustment for “optimal cutoffs” or the inappropriate use of bioinformatic techniques (4). Moreover, integrating biomarker studies in the conventional approach of clinical drug development presents inherent limitations. New drugs are initially developed in patients with advanced metastatic disease, with remarkable shortcomings in the collection of tumor specimen. Studies with “re-biopsy” or even with serial biopsies have been successfully conducted in metastatic solid tumors (5), but ethical and practical issues related to additional invasive procedures represent a major limitation, especially when biopsies are mandatory and raise the ethical issue of bargaining treatment opportunity for tissue specimens. Therefore, collection of tumor tissue almost always dates back to the time of the initial diagnosis, introducing the bias of associating clinical response in a metastatic stage with initial biological tumor characteristics that, especially after previous treatments, may have changed profoundly. At a time when the development of noninvasive biomarker (eg, in serum or plasma) is still immature (6), the model of preoperative systemic therapy represents an opportunity whereby the above listed issues find a feasible and acceptable solution.

Advantages of the Neoadjuvant Setting for Discovering, Developing, and Validating Biomarkers

For discovering and developing predictive biomarkers, randomized phase II neoadjuvant trials represent the ideal setting for many reasons. As routine practice, tumor samples are collected for diagnosis and after drug therapy at surgery. The accessible tumor location in the breast cancer makes additional biopsies during therapy feasible at a minor risk. Pathological complete response and other pathological measurements (7,8) have been consistently associated with long-term survival and may be useful as surrogate endpoints in developing and evaluating both predictive and surrogate biomarkers. Even though targeted therapies are highly effective in a variable small proportion of patients, they are usually developed in combination with standard treatment in an “add-on” strategy. A
A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention

Baseline measurements that indicate whether the patient is likely (or unlikely) to benefit from a specific drug or regimen

Provides evidence about the biological effect of a drug; requires both a baseline and a further assessment; when it is used for establishing that a drug inhibits its intended target, it could provide a “proof of target effect”

A characteristic or variable that reflects how a patient feels, functions, or survives and which reflects the effect of a therapeutic intervention

The demonstration of prolongation of life or improved health-related quality of life (or an established “surrogate” for at least one of these)

The improvement over the baseline in any clinical endpoint (ie, clinical and pathological response in neoadjuvant setting)

Any assessable and desirable biological effect of a drug

A pharmacodynamic biomarker or other clinical assessment that changes over the time for the treatment effect (causality relationship), that is intended to substitute for a clinical endpoint like overall survival or improved health-related quality of life (as such, also referred to as “intermediate clinical endpoints”)

Table 1. Definitions of terms used to describe disease measurements and treatment effect

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Biomarker</td>
<td>A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention</td>
</tr>
<tr>
<td>Predictive biomarker</td>
<td>Baseline measurements that indicate whether the patient is likely (or unlikely) to benefit from a specific drug or regimen</td>
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<tr>
<td>Pharmacodynamic biomarker</td>
<td>Provides evidence about the biological effect of a drug; requires both a baseline and a further assessment; when it is used for establishing that a drug inhibits its intended target, it could provide a “proof of target effect”</td>
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<tr>
<td>Clinical endpoint</td>
<td>A characteristic or variable that reflects how a patient feels, functions, or survives and which reflects the effect of a therapeutic intervention</td>
</tr>
<tr>
<td>Efficacy</td>
<td>The demonstration of prolongation of life or improved health-related quality of life (or an established “surrogate” for at least one of these)</td>
</tr>
<tr>
<td>Clinical activity</td>
<td>The improvement over the baseline in any clinical endpoint (ie, clinical and pathological response in neoadjuvant setting)</td>
</tr>
<tr>
<td>Biological activity</td>
<td>Any assessable and desirable biological effect of a drug</td>
</tr>
<tr>
<td>Surrogate biomarker/endpoint</td>
<td>A pharmacodynamic biomarker or other clinical assessment that changes over the time for the treatment effect (causality relationship), that is intended to substitute for a clinical endpoint like overall survival or improved health-related quality of life (as such, also referred to as “intermediate clinical endpoints”)</td>
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randomized trial comparing the standard and the combined regimen will only allow for investigating biomarkers predictive of the additional benefit of the targeted therapy over the standard treatment but will be useless for defining predictors of benefit from the targeted therapy alone. Neoadjuvant trials enriched for target-positive disease (ie, HER2-positive) may also include treatment arms that apply biological agents without additional chemotherapy to investigate their efficacy but more importantly to define predictive biomarkers and eventually identify those patients who do not need treatment with toxic chemotherapy. This approach was successfully undertaken in the NeoSphere trial where the combination of the HER2-directed monoclonal antibodies trastuzumab and pertuzumab resulted in 17.8% of pathological complete response (9).

In another relevant investigational twist to the concept and practice of primary systemic therapy, patients who are not candidates for neoadjuvant treatment can take part in studies of so-called “presurgical therapy,” also known as window-of-opportunity studies. Patients receive the treatment for a brief interval before surgery, and the effect of the intervention on the tumor will be assessed by comparing the surgically removed sample with the diagnostic biopsy sample. This approach has been successfully used to evaluate the effect of a selective estrogen receptor modulator (idoxifene) on biological markers of cell proliferation and apoptosis (10) and to evaluate the epidermal growth factor receptor inhibitor erlotinib during the immediate preoperative period to measure the antiproliferative and/or proapoptotic effect in the posttherapy specimen (11). As a final consideration, randomized phase II neoadjuvant trials with biomarker stratified or enrichment designs (12) could quickly validate predictive biomarkers and explore their clinical utility before conducting large randomized phase III adjuvant clinical trials.

How to Select Candidate Biomarkers for Clinical Development of Targeted Therapy with Companion Diagnostics

The successful development of trastuzumab in breast cancer has pivoted around a key characteristic: the definition of a candidate predictive marker (HER2 overexpression) and the implementation of clinical studies restricted to patients bearing HER2-overexpressing breast cancer as assessed in centralized assays and, after the pivotal study was successfully completed, in companion immunohistochemistry diagnostic tests like the HercepTest (DAKO, Carpinteria, CA) or the CB11 (Ventana Medical Systems, Tucson, AZ). As already pointed out, this combination of predictive markers and new drug development is rare. The successful discovery of useful biomarkers cannot rely only on clinical data and almost always requires the selection of reliable preclinical candidates. One strategy is gaining some room is the search for candidate predictive biomarkers or gene expression signatures in preclinical models (such as cell line and animal xenograft) that are later tested and eventually validated in clinical trials, thereby reducing the number of patients required for tissue collection (13). As an example, gene signatures associated with response/resistance to the Src inhibitor dasatinib have been developed and might be useful for the selection of patients candidate to the drug (14). However, reliability and reproducibility of results derived by this approach have been more recently challenged (15). Another option being pursued is to focus on pathway-specific biomarkers, given that most targeted therapies inhibit well-characterized molecular pathways. The activation state of many pathways can be assessed directly by probing the state of downstream substrates in the pathway. Indirect approaches might also be possible using gene expression signatures. As an example, pathway activation in cell lines engineered to express specific oncogenes have been associated with specific gene expression signatures (16), and a signature associated with loss of PTEN has been confirmed in breast cancer tumors (17). Finally, genotyping of tumor DNA for mutations and fusion genes has been found to be useful for predicting responses to targeted therapies in lung cancer, gastrointestinal stromal tumor, glioblastoma multiforme, and chronic myeloid leukemia, but the relevance in breast cancer is unclear so far, even though the development of PI3K inhibitors may reveal a similar scenario in case of PI3K mutations (18).

Surrogate Markers for Activity and Efficacy

Changes in Ki67 labeling index in response to short-term challenge with a hormonal treatment (either tamoxifen or aromatase inhibitors)
have been proposed as a surrogate marker of clinical activity and perhaps efficacy according to the association with longer disease-free survival (8). Two neoadjuvant trials demonstrated a more significant decrease of Ki67 either with letrozole or anastrozole compared with tamoxifen (19,20), and results of the assay were in keeping with the superiority of both aromatase inhibitors in the adjuvant setting. A randomized phase II neoadjuvant study comparing fulvestrant at the approved dose (250 mg/mo) with a high-dose regimen (500 mg) provided evidence for increased downregulation of Ki67 with higher dose (21). The result again was in line with the observation that high-dose fulvestrant was superior to standard dose in women with metastatic disease. Despite these encouraging results, the potential advantages of using pharmacodynamic and surrogate markers for clinical drug development and for the tailoring of targeted therapies has largely been disappointing and, so far, restricted to hormonal treatments.

### Suggested Predictive Markers for Tailoring Targeted Therapies

Suggested predictive markers for different classes of targeted agents based on in vitro (preclinical) or clinical data are summarized in Table 2. Because of the not-completely-overlapping mechanism of action and resistance between trastuzumab and lapatinib, there is great interest in defining specific predictive biomarkers, especially because this resistance could be potentially overcome by new drugs under clinical development. p95HER2 was associated with trastuzumab resistance but not lapatinib in vitro, as well as in a small number of patients (22). Phosphorylated HER2 and HER3 were highly predictive of response to lapatinib in a retrospective correlative phase II study in inflammatory breast cancer (23). Uregulation of the PI3K pathway is an important determinant of resistance to HER2-targeted therapy with activating mutations in genes encoding the PI3K catalytic domain and loss of PTEN being the most common mechanisms of PI3K pathway hyperactivation (24). PI3K pathway signaling is also a target for specific inhibitors. PIK3CA mutations were more common in hormone receptor–positive (34.5%) and HER2-positive (22.7%) than in basal-like tumors (8.3%). AKT1 (1.4%) and PTEN (2.3%) mutations were restricted to hormone receptor–positive cancers (25). BRCA1 and BRCA2 germinal mutation and triple-negative molecular subtype have been suggested to be predictive of sensitivity to poly (ADP-ribose) polymerases inhibitors (26).

### Conclusions

Targeted therapies can either be extraordinary achievements capable of influencing the chances of a cure in selected patients, or can stay an unfulfilled promise with an exceptionally modest benefit for an exorbitant cost. The development of predictive and surrogate biomarkers to identify subgroups of patients who will likely benefit from a drug would be more cost-effective than looking for small differences in large unselected groups. The option of neoadjuvant treatment offers a great opportunity to achieve this goal. However, paradigms, objectives, methods, and regulations of clinical trial designs have to adapt to such a potential role for neoadjuvant therapy, which should substitute the setting of metastatic disease early on in drug development.

### References


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