Bridging the Gap Between Translational Research and Clinical Application

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Protocols employing primary systemic therapy provide important basic knowledge about tumor behavior/response to therapy, but major challenges remain in how to obtain and use this information practically in the clinical setting.

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Primary systemic (or neoadjuvant) therapy can provide major clinical benefit by reducing the size of primary breast tumors in cancers responsive to treatment (1). However, neoadjuvant therapy also provides major opportunities for translational research because tumor responses to therapy may be monitored by measuring/sampling the primary tumor (2). This review will 1) discuss the challenges encountered when performing translational research in the neoadjuvant setting and 2) identify issues that need to be addressed in moving results into clinical practice.

Neoadjuvant Protocols

In the neoadjuvant setting, therapy is given before surgery to the breast (1,2). This has advantages in that the primary tumor is available for biopsy (sometimes on sequential occasions) and accurate assessment of response. Therapy is usually reserved for patients with large cancers, with the hope of shrinking the primary tumor so that it becomes operable or amenable to conservative treatment (1). While surgical endpoints constitute immediate benefits, there are other potential advantages. For example, knowledge of response of the primary tumor during short-term treatment might be used to plan longer adjuvant therapy (3). Additionally, the approach forms an important research model by which to understand the nature of tumor response and the mechanism of drug action (4). An example of such a research protocol is illustrated in Figure 1; this has been used in work in which gene expression has been related to response/resistance to endocrine therapy (5). Molecular markers measured in biopsies of primary tumors before and during treatment while monitoring tumor size may be correlated to pathological and clinical changes. This protocol will be used to illustrate the complexities and challenges encountered in performing translational research—while the general design of neoadjuvant protocols is simple, there are confounders and issues that need to be addressed before meaningful results are obtained and observations can be applied clinically.

Objectives

Translational neoadjuvant therapy studies generally have the following aims: 1) prediction of response/resistance to treatment, 2) identifying response to particular treatments with the intention of employing them adjuvantly, and 3) prediction of long-term outcome. These objectives have challenges in common (discussed in the following sections). However, aims (2) and (3) have the following confounder: Adjuvant therapy and long-term outcome are determined by micrometastatic disease, which may have different behavior and response to therapy to the primary tumor as assessed in neoadjuvant protocols (6,7).

Nature and Assessment of Response

Different endpoints may be assessed in neoadjuvant protocols including measurements of clinical size, histopathology, proliferation, and molecular markers. These are not equivalent and have individual advantages and limitations.

Clinical measurements are generally used to determine response, particularly if neoadjuvant therapy is being given to reduce tumor size. Size may be measured using calipers, by mammography or by ultrasound. Discrepancies are not infrequent between the methods, but tumor size on excision correlates best with ultrasound (8).

Pathological response following neoadjuvant chemotherapy is a powerful determinant of long-term outcome: Complete pathological response is significantly associated with better disease-free and overall survival (9). However, complete pathological responses to neoadjuvant endocrine therapy are rare (10), although changes in tumor morphology and histology are evident in 60%–80% of tumors after 3–4 months of treatment (11,12). Assessment of partial response is needed but such scores are often subjective and confounded by tumor sampling. Rates of clinical and pathological responses are often similar and associated, but the concordance is far from absolute, and about 20% of tumors display a discordant phenotype (13).

Decreases in tumor proliferation often occur following neoadjuvant treatment (12,13). They may be observed very early into treatment preceding clinical/pathological response (13) and can be positively and significantly correlated with clinical and pathological response (13,14). However, the various forms of response are not equivalent. Thus, clinical and cell cycle responses to both tamoxifen and letrozole can be discordant in over a third of cases (14), and proliferative response is not quantitatively different in cases clinically responding or resistant to anastrozole (15).
Molecular responses to neoadjuvant therapy have been elicited following neoadjuvant treatment as detected by immunohistochemistry (12,13,16–18) and microarray studies (17,18). These changes in gene and protein expression have not been adequately correlated with clinical, pathological, and proliferative parameters but may be potential surrogates for more established outcomes.

**Duration of Treatment/Time of Assessment**

Neoadjuvant therapy is usually given for 3–4 months (1) based upon allowing sufficient time for meaningful tumor shrinkage in responding cases and not persisting with ineffective treatment in resistant tumors. However, individual tumors respond in different time frames, and the same time-point of assessment in all may lead to misclassification of response in some. Thus, neoadjuvant tamoxifen can reduce tumor size within a month of treatment, but clinical response is not apparent in most cases until 2–3 months (in a few, shrinkage may not occur until 3–6 months) (19). Treatment beyond 3 months is occasionally associated with regrowth of initially responsive tumors. Markers of response may therefore differ according to time of assessment, some predicting for early but not late response and vice versa.

Measurements are often made in pretreatment biopsies with the intention of relating results to endpoints evaluated after treatment. These evaluations are potentially predictive but do not directly assess the effects of therapy. Histochemical or molecular measurements in biopsies taken early into treatment (eg, 10–14 days) (5,20) may precede and be predictive of later pathological and clinical changes. However, a single early on-treatment sample does not discriminate between the marker level resulting from treatment or being present before treatment. A dynamic approach comparing sequential biopsies taken before and early into treatment is more informative and gives a better understanding of interactions between treatment and tumor biology (5,17,18).

**Tumor Selection**

Not all tumors are candidates for neoadjuvant treatment. Small cancers are likely to be treated by immediate surgery; changes in volume are also imprecise in tumors less than 3 cm.

Certain pathological tumor subtypes are also best excluded from neoadjuvant studies. Mucinous tumors are difficult to assess for response because change (or lack of change) in tumor size may reflect mucin content rather than malignant burden. Tubular cancers have such a good outcome that the patients should not be exposed to systemic therapy.

**Nature/Heterogeneity of Tumor Samples**

Neoadjuvant protocols often employ core and excision biopsies (21). Excision biopsies provide adequate tumor for relatively extensive analyses, but they may compromise assessment of subsequent response and preclude sequential sampling. Core and needle biopsies avoid these difficulties, but small size may limit analysis, be associated with sampling errors relating to tumor heterogeneity and provide challenges for histopathological assessment. There can be systematic differences between results obtained from excision and core biopsies (21)—generally, excision biopsies are more representative than cores. The act of tumor sampling can have profound biological effects, which need to be considered when timing further assessments and sampling.

**Tumor Diversity**

Diversity between tumors represents a major challenge. Although tumor series are generally carefully selected for size and pathology, diversity often remains in terms of molecular phenotype (5,17,18) and response status (5,15,16). Treatment effects on growth rate, pathology, proliferation, and molecular profiles may be equally diverse (even in clinically resistant tumors, treatment can be associated with a spectrum of molecular changes) (22). This has important clinical implications in terms of 1) the number of cases required to take account of diversity, 2) the need to analyze data on a group basis despite the objective of prediction in the individual, and 3) the corresponding diversity of treatments that might be used for specific tumors.

**Individual Prediction vs Group Comparison**

The objective of tailoring treatment on an individual patient basis is rarely achievable; management is usually founded on allocating individual patients to a group with estimated likelihood of clinical benefit. Because individual tumors can be sampled and monitored, the hope is that clinical, pathological, and molecular features might be used to produce robust predictive indices of clinical benefit and outcome. However, for validation, it is essential to demonstrate that observations do not result from chance. This invariably entails group analyses of large tumor numbers before meaningful conclusions can be applied to individual cases. In practice, an algorithm/index needs to be developed first which can provide some odds of clinical benefit rather than absolute certainty. These estimate probability of clinical outcome empirically from accumulated data. This approach has been used in some prognostic classifiers (23).

**Translation to Clinic**

The above sections and Table 1 highlight some of the challenges encountered in performing translational research on clinical material
Table 1. Neoadjuvant protocols—challenges for translational research

Clear definition of objectives
- Prediction of response/resistance to treatment
- Identifying response to particular treatments - subsequent adjuvant use*
- Prediction of long-term outcome*
  * Confounded by potential differences between primary and micro-metastatic disease

Nature and assessment of response
- Clinical
- Pathological
- Proliferative
- Molecular
  * Not equivalent

Duration of treatment
- 3–4 mo
  * Misclassification of response in late responders
  * Marker indices may differ according to time of response

Time of assessment
- Pretreatment biopsy
  * No direct assessment of treatment effects
  * Lack of discrimination between treatment effects and presence before treatment
- Sequential biopsies
  * More difficult to obtain

Tumor selection
- Small tumors
  * Difficult to measure size accurately
  * Special pathological types, eg, mucinous and tubular
  * Difficult to measure response, not suitable for neoadjuvant therapy

Nature/heterogeneity of tumor samples
- Excision biopsies
  * Compromise tumor measurements
- Core biopsies/FNA
  * May not be representative

Tumor diversity
- Clinical response
- Pathology
- Molecular phenotypes and responses
  * Increased numbers of study cases

Individual predictions vs group comparison
  * Different data handling and needs for odds of benefit/certainty

Challenges in moving research into clinics will be enormous, especially if the oncologist’s need is to make management decisions in all patients but on an individual basis. Clinicians are faced with greater spectra of patients than the researcher who is likely to have selected his cases to simplify complexity and produce a degree of homogeneity from which statistically significant relationships may be discerned. Consequently, many patients routinely presenting will be excluded from the research algorithms. Even within a relatively homogenous group of patients receiving uniform treatment, practical considerations of retrieving high-quality biopsies and accurately assessing response mean that many patients are not evaluable.

Other practicalities relate to recruiting a team of specialist experts and undertaking sophisticated research methodology. Costs may be prohibitive and technologies such as genome-wide microarrays impractical. Ideally, a discriminator comprising a few variables that can be evaluated on fixed material is required, but the signs are that this may not be immediately possible. For example, our multigene signature that can discriminate between tumors clinically responsive and resistant to letrozole comprises over 200 variables (3); the use of a small number of the most informative genes is associated with a marked loss of discrimination.

The gap between translational research and clinical application is formidable, and bridges are embryonic. However, an understanding and realistic assessment of the challenges represent sound foundations.

References
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