

Novel Pharmacodiagnosics in Breast Cancer

a report by

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Pharmacodiagnosics is an expanding discipline with major potential for improving patient care during the early part of the 21st century. The principle behind pharmacodiagnosics is the specific linking of a treatment outcome (response/toxicity/resistance) to a key molecular alteration, e.g. protein overexpression or gene amplification, within a disease state to predict therapeutic response.

Pharmacodiagnosics has utility in measuring response (efficacy) or adverse side effects (safety) for both established and novel therapies. In oncology, recent advances with targeted therapeutics have demonstrated the critical importance of appropriate pharmacodiagnostic approaches. Pharmacodiagnosics based on identifying somatic molecular changes in the tumour form the basis of molecular targeting of many novel therapies. The development of Herceptin (targeting the human epidermal growth-factor receptor (HER2) oncogene in breast cancer) and Gleevec (targeting breakpoint cluster region-Abelson tyrosine kinase (BCR-ABL) translocation in leukaemia) are excellent examples of the close relationship between target expression, pharmacodiagnostic tests and clinical therapeutic response.

However, despite significant research efforts over the past 20 years, with literally hundreds of thousands of research publications relating to prognostic and predictive markers of response, relatively few predictive or pharmacodiagnostic assays are internationally accepted as of value in patient management and treatment selection. For example, in breast cancer only two pharma-codiagnostic tests are currently linked to targeted therapy: tumour expression of oestrogen receptor (ER), and HER2, linked to tamoxifen and Herceptin treatment, respectively. This contrasts with clear evidence that breast cancer represents a spectrum of different molecular disease types, each of which has the potential to respond to different therapeutic approaches. There is currently an urgent need to develop appropriate tests to stratify patients for targeted therapy to ensure that these novel agents are given to patients who are most likely to respond. By

focusing on the potential for novel pharmacodiagnostic tests in breast cancer, the authors highlight the key steps in meeting the challenge of successfully developing and implementing novel pharmacodiagnosics in the clinical setting.

Current Pharmacodiagnostic Tests

During the last 50 years clinicians have relied predominantly on the anatomic and morphologic classification of tumours to predict outcome (prognosis). Stratification of breast cancer patients, using indices such as the Nottingham prognostic index and adjuvant online provide support for decisions relating to treatment. However, these indices do not directly take into account the molecular changes that occur within tumours. The first use of pharmacodiagnosics in breast cancer occurred in the 1960s and 70s with the discovery that the response of post-menopausal women to endocrine-based therapy (most often tamoxifen) was limited to ER-positive breast cancers. The synergy between pharmacodiagnosics and patient benefit from a linked targeted therapy was, however, almost forgotten prior to the introduction of Herceptin in the late 1990s. Herceptin targets HER2 and pharmacodiagnostic profiling of tumours was essential for patient stratification since only patients whose tumours have HER2 overexpression and/or gene amplification respond to Herceptin treatment.

The recent implementation of Herceptin and its linked pharmacodiagnostic test into clinical practice challenged the 'one-size-fits-all' treatment strategy that has existed among researchers and clinical oncologists for many years. The focus of the majority of clinical trials is to treat all breast cancer patients with the same drug without taking into account molecular differences that may select for response to such agents. This one-size-fits-all strategy ignores the possibility that the patients responding to novel treatments (reflected by an apparent overall improvement in outcome) may present with tumours with a different molecular profile to those responding to the previously accepted treatment and may therefore represent a different group of patients

altogether. While this is unlikely to be the case in all instances, there is a clear risk that such a strategy has improved treatment for one group of patients at the cost of reducing treatment efficacy for others.

Knowledge and understanding of the molecular mechanisms that underpin cancer development and progression have expanded in the last few years. The pharmaceutical and diagnostic industries, as well as scientists and clinical oncologists, have therefore become more aware that the use of pharmacodiagnostic tests to identify *a priori* patients who will respond favourably (or unfavourably) to a linked targeted treatment provides a huge potential for improving cancer treatment efficacy. Optimal expenditure of healthcare resources will depend on the availability of appropriate pharmacodiagnostic tests for selection of patients who are most likely to benefit from novel molecular-targeted treatments (which tend to have a high financial cost and a high potential benefit). Patients will clearly benefit from the use of pharmacodiagnosics, as such tests will maximise the likelihood of patients being allocated the most effective treatment for their tumour type.

Identifying Novel Predictive Markers

With a clear improvement in the biological knowledge of breast cancer and the change of focus from the one-size-fits-all strategy to the use of targeted cancer therapies, there is reason for significant optimism regarding identification and validation of novel predictive markers (pharmacodiagnosics). However, there is also evidence that previous approaches to the identification and validation of such pharmacodiagnosics has been lacking in focus. Significant numbers of publications relating to potential predictive and prognostic markers in breast and other cancers have not resulted in the implementation or final exclusion of these candidates. The methodological quality and clinical relevance of many such studies are open to question and multiple studies of the same marker often lead to different conclusions. This is often the result of variations in methodology, poor study design, lack of reproducibility within the assay, and inappropriate or misleading statistical analysis due to statistically underpowered studies. In the past, identification of predictive markers has also been restricted by confusion in the definition of 'predictive' and 'prognostic' factors. Prognostic markers are of value in defining the risk of recurrence and death from disease, in patients (usually untreated) who are being considered for treatment. Prognostic markers can aid in the decision-making process by allowing the risk of therapeutic approaches to be balanced against the benefits for the patient. These markers are therefore of value in deciding whether to treat patients

conservatively or aggressively. Conversely, predictive markers identify patient subgroups, selected for a particular therapeutic approach, who are likely to benefit from specific therapies where the likelihood of response is linked to the predictive marker.

Validation of Novel Pharmacodiagnosics – A New Approach

One of the central problems in validation of novel pharmacodiagnosics has been the lack of clear strategies and guidelines for the development of such tests. There is currently no clear measure of the 'success' of a novel test other than approval by health authorities such as the US Food and Drug Administration (FDA). The lack of such guidance, to both companies and researchers, has significantly hampered development in this area. A more rigorous application of scientific principles is clearly required. A broadly similar approach was taken, around 40 years ago, to the design and structure of clinical trials, with agreed measures of toxicity, performance status and response being applied to a structure of phase I, II and III clinical trials required for the implementation of novel therapeutic approaches. A similar consensus is approaching regarding the validation of novel predictive and prognostic markers, with proposals for standards of reporting of specific marker studies and a 'road-map' relating to the development of novel predictive markers. Such approaches are essential if rapid development of novel markers is to gain international acceptance. These road-maps are based on common criteria for identification, validation and implementation of novel pharmacodiagnosics. With regard to novel pharmacodiagnosics, the test must satisfy a number of quality-related criteria:

- The test should be easy to apply in a conventional clinical setting and provide results that can be easily understood by the clinician and relied on by the patient.
- The assay must be as simple as possible and provide a precise measurement of the marker in question.
- The test should be reproducible and include given thresholds for marker 'positivity' and 'negativity'.
- Where possible the test should be validated in a well-characterised tumour bank with linked clinical patient information relevant for the treatment-marker interaction under investigation and assay performance as predictor of treatment response defined in this context.

These studies also provide information regarding sample size and assay cut-offs to achieve the best

selection of patients that will respond to the particular treatment.

The fact that only a few pharmacodiagnostic tests linked to targeted therapy have been internationally accepted for use in breast cancer could be regarded as a poor repayment for the investment of many years of basic and clinical research. Despite an improved understanding of the molecular pathways underlying cancer our ability to use clinically validated pharmacodiagnostic tests to target therapies, which clearly have molecular determinants of tumour response, has lagged behind progress in other areas. Given the rapid expansion of development of targeted therapies there is a need for faster and more successful clinical integration of current development of targeted therapies and the pharmacodiagnostic assays. Such a process is likely to involve closer collaboration between clinical oncologists, pathologists, and scientists as well as pharmaceutical and diagnostic companies. Such teamwork will benefit from the diverse opinions and experience of these relevant and involved parties, each with different backgrounds, expertise and interests. Each approaches the question from different angles but with the same ultimate goal.

While some pharmaceutical companies have started to use pharmacodiagnosics in phase I and II clinical studies to predict patient response in the context of drug efficacy and safety, not many companies have the core capabilities, or regard it as their key mission, to develop pharmacodiagnostic tests into clinically validated and approved predictive markers of patient stratification. On the contrary, diagnostic companies, which may lack experience in identifying novel targeted therapies, have extensive experience in working with local pathology services to ensure that pharmacodiagnosics are 'fit for purpose' in today's clinical diagnostic environment, but may lack the facilities to screen multiple potential markers for use as pharmacodiagnosics. With expectations that future cancer therapies will be given to a smaller subgroup of patients, teamwork between drug and diagnostic industries becomes even more critical to raise the quality of research and decrease the time taken to deliver novel products to patients. The future challenge for industry will be to develop clinical trials that include both testing of novel targeted therapies and linked pharmacodiagnostic tests that identify the subset of patients who are most likely to respond to the therapy. Such an approach must be underpinned by collaboration between industry, academia and clinical specialists. Strong collaboration between clinical researchers and industry provides an opportunity to accelerate the identification and validation of novel predictive markers to select

patients likely to benefit from targeted therapies. Clinical and translational research provides the opportunity to both validate pharmacodiagnostic tests and appropriately target novel agents.

For academia, particularly diagnosticians and clinicians, the appropriate diagnosis and classification of the tumour is of key importance for the selection of the most appropriate treatment. This process can be facilitated by collaboration with multinational companies who have the resources to ensure international integration into clinical practice of novel pharmacodiagnostic tests, which will accelerate delivery of targeted therapies to patients worldwide. Such collaboration can therefore be a tool by which clinicians and diagnosticians can ensure the appropriate scientific rigor for the proper use of a pharmacodiagnostic test and the linked therapy to safeguard and accelerate improvements in patient care.

The outcome from such collaboration, in this new era of targeted therapies, is likely to be accelerated validation and targeting of novel treatment approaches, which both improves patient care and allows successful marketing of novel products.

Conclusion

Pharmacodiagnosics is an expanding discipline with a major potential for improving clinical patient care in the future. Increased knowledge of tumour biology and the recent use of targeted therapy have recently challenged the one-size-fits-all strategy for cancer treatment. Major progress has been made to identify novel targeted therapies, but the progress in identifying pharmacodiagnosics linked to these targeted therapies is still very slow and only a few pharmacodiagnosics have so far successfully been internationally accepted and applied in clinical practice. As treatment response depends on the molecular profile of the individual cancer, the major challenge for the future will be to co-develop novel targeted therapies and pharmacodiagnostic tests that will predict patient response to therapy. High-quality research has shown that markers predictive of treatment response can be taken from the laboratory to the bedside. However, to successfully integrate novel pharmacodiagnosics into clinical practice the collaboration between pharmaceutical and diagnostic industries, clinical oncologists and researchers must be strengthened. With successful teamwork, however, it is expected that the use of pharma-codiagnostic tests will be more widely recognised and the number of tests linked to targeted therapies will significantly increase. ■

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