Interpreting Cancer Biology: Refining Our Therapeutic Algorithm in Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

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INTRODUCTION

The last 40 years have seen significant advances in our knowledge of breast cancer, fuelling the development of a succession of effective new therapies that have led to improved outcomes for the breast cancer patient. Crucial to these advances has been the application of an ever growing armamentarium of molecular technologies, which have identified multiple discrete types of breast cancer, each with their own distinct biology which can provide viable targets for therapeutic intervention. In this issue of *The Oncologist* (European Edition), *European Perspectives* begins a series that will outline the current state-of-the-art in our understanding of breast cancer and its clinical management. This series will emphasise the influence of breast cancer biology and the interpretation of breast cancer genomics on patient care, while also addressing the significant issues of cancer survivorship and fertility that are of vital importance to the quality of life of both postmenopausal women and the young breast cancer patient. These articles will be complemented by online interviews and debates with key international opinion leaders, providing a combined resource for our readership that seeks to critically review the salient advances, challenges and opportunities encountered by oncology health care professionals in treating this common malignancy.

UNDERSTANDING BREAST CANCER: THE IMPACT OF THE MOLECULAR REVOLUTION

In 1987, Denis Slamon and colleagues published results that linked the amplification of one particular gene, the HER-2/neu (*ErbB2*) oncogene, to reduced survival in breast cancer [1], providing the conduit for the development of the first targeted therapeutic approach in cancer based on a molecular genomic abnormality. This seminal paper utilised Southern blotting, the molecular technology of that era, to define a 2–20 fold amplification of *ErbB2* in approximately 30% of the

189 tumour samples from breast cancer patients. The intervening 25 years have witnessed a profound technological revolution. The application of DNA sequencing and polymerase chain reaction (PCR) approaches have informed identification of individual gene contributions to breast cancer pathology, while gene expression profiling has allowed us to paint "real time" molecular portraits of the activity of thousands of genes inside the breast cancer cell [2, 3]. This explosion in our knowledge of breast cancer biology reached its apotheosis in the recent publication in matched cancer/normal tissue of the complete exome sequence from 103 breast cancer patients and the whole genome sequence of 23 cancer/normal pairs [4].

MANIPULATING BREAST CANCER BIOLOGY FOR THERAPEUTIC BENEFIT

Interrogation of the biology of the breast cancer cell has underpinned our efforts to develop new therapeutic opportunities that can bring significant benefit to women with breast cancer, as exemplified by the translation of *Her2* biology to herceptin therapy. Identification of hormone receptor (HR)-positive breast cancer patients expressing the estrogen receptor (ER) prompted the use of hormone manipulation approaches, initially with tamoxifen, an antagonist of the ER, but more recently by the employment of a number of specific aromatase inhibitors, including anastrozole, letrozole, and exemestane, which are used as first-line endocrine treatments in HR-positive metastatic disease [5]. The recent Southwest Oncology Group (SWOG) trial 75764, combining anastrozole and fulvestrant in metastatic breast cancer, emphasises how precise biological knowledge of cancer signalling pathways can advance successful therapeutic development. In this phase III randomised trial, the combination of two agents that selectively target different aspects of estrogen production in postmenopausal women was employed for therapeutic benefit [6]. Anastrozole is an aromatase inhibitor that blocks the conversion of androgens to estrogens. Fulvestrant is an analogue of estradiol that disrupts estrogen-receptor dimerization, thus increasing degradation of the ER while also reducing growth factor signalling crosstalk, thus potentially combating the development of resistance. Combining these two agents, which target different aspects of ER signalling, significantly delayed the development of progressive disease, demonstrating

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the superiority of a combination approach and providing a rationale for a new standard of care in this breast cancer subset.

BREAST CANCER IN YOUNG WOMEN: CAN AN UNDERSTANDING OF BIOLOGY HELP?

Although we are making significant progress in improving breast cancer outcomes, recent data indicate that there is a worrying increase in aggressive breast cancer in young women. Analysing the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database for the period 1976–2009, Johnson et al. found a significant increase in metastatic breast cancer in women aged 25–39 when compared to older women [7]. Just as disease biology has influenced our clinical management of the postmenopausal patient, an increased understanding can also underpin the clinical decision-making process in breast cancer in young women. In this issue of *European Perspectives*, Colleoni and Anders debate whether the biology of breast cancer in young women is unique and how this knowledge influences our provision of care, particularly given the aggressive breast cancer phenotype that is overrepresented in this patient cohort [8].

DISSECTING THE MOLECULAR AND STATISTICAL COMPLEXITY OF THE BREAST CANCER GENOME

While the 'omics revolution has allowed unparalleled access to the breast cancer genome, the molecular complexity that it has uncovered can appear overwhelming. Distinguishing the key “driver” mutations from the background noise of multiple “passenger” variants represents a defining challenge for molecular medicine. An additional barrier to successful application of discovery biology is the integration of genome-scale information generated by diverse technologies. For example, in breast cancer, how do we interpret the data generated from the nonoverlapping technologies of gene expression profiling and copy number variation analysis? Addressing this issue requires a systems medicine approach, where integrative data handling algorithms can allow core biological pathways to be linked to clinical subtypes [9, 10], thus providing a rationale for identifying new targets.

Appropriate statistical analysis of 'omics data is also of paramount importance. In this instalment of *European Perspectives*, Kelly et al. emphasise that the undoubted increased power of gene expression profiling brings its own unique challenges and the application of appropriate statistical rigour is essential to ensure accurate interpretation of results [11]. It should be stressed that defining precise molecular algorithms that interpret the complex biology of

breast cancer and translating this knowledge into new therapeutic approaches using molecular stratification require extensive bioinformatics expertise and capacity.

TRANSLATING BIOMARKER DISCOVERY TO DIAGNOSTIC APPLICATION

A final consideration for defining new treatment algorithms in breast cancer is the translation of biomarker discovery to diagnostic application. In this era of targeted therapy, companion diagnostics increasingly are being required for molecular stratification of breast cancer patients for personalised medicine approaches. The US Food and Drug Administration (FDA) have emphasised that the development of new drugs must include an accompanying companion diagnostic [12, 13], with the European Medicines Agency (EMA) also beginning to adopt similar policies [14].

Use of gene expression profiling approaches [15, 16] has identified prognostic signatures that have been converted into validated tests (Oncotype DX, MammaPrint) with clinical application. These “molecular predictors” have allowed precise definition of responders and nonresponders based on their molecular classification [17], thus sparing women who do not require it the debilitating effects of chemotherapy. However, while these prognostic tests have been widely available and reimbursed in the US and Canada, it was only in 2012 that Ireland became the first European country to fully reimburse for the use of Oncotype DX [17], although provisional approval for its use has recently been published by the National Institute for Clinical Health and Excellence (NICE) in the UK [18].

CONCLUSION

Manipulating breast cancer biology for therapeutic benefit represents the “holy grail” for improved clinical outcomes in this common disease. Precise dissection of the breast cancer genome utilising diverse discovery platforms is providing an unprecedented level of information with diagnostic and therapeutic potential. Integration of this 'omics knowledge using systems medicine approaches will inform the development of new targeted therapeutic approaches. Complementing these therapeutic advances with precise predictive, prognostic and early response biomarker diagnostics is underpinning a new therapeutic algorithm for the breast cancer patient.

DISCLOSURES

Gabriel Hortobágyi: Antigen Express, Galena Biopharma, Novartis, Rockpointe (C/A); Novartis (RF); Taivex (O); founder and member of the board of directors for Citizen's Oncology Foundation.

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