Expert Opinion: Future Frontiers and Challenges in Cancer Medicine

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This Expert Opinion piece highlights the transformational changes that need to occur in cancer treatment in the era of molecular stratification and targeted therapy. An increased understanding of cancer biology, coupled with the implementation of precise “-omics” technologies, has revealed that cancer can now be considered to be a heterogeneous disease. Our historical “one size fits all” therapeutic approach is, therefore, no longer valid, and new treatment algorithms must be developed and tested rigorously in selected patient populations. This has significant implications for the different stakeholders involved, including the patients, the health providers, the health services/health insurers, and the pharmaceutical industry. We will examine how the changing clinical paradigm in cancer medicine and its challenges must be addressed in order to provide an overarching translational cancer medicine blueprint for cancer patient treatment.

The First Challenge: Redefining Cancer in the Molecular Age

Translating new biological knowledge into more effective cancer diagnostics and therapeutic interventions is a major challenge. With today's rapid pace in scientific and technological discovery, we must functionally link basic and clinical research with drug discovery, molecular diagnostics, and next generation clinical trials in order to maximize the benefit from these new developments for the cancer patient. Our first challenge is in our evolving definition of disease. Historically, we have characterized cancer mainly in relation to its anatomical location and associated pathology/histology. While this has provided valuable diagnostic information underpinning real advances in clinical care over the last 40 years, more recently the introduction of “transformational” molecular-based technologies has significantly enhanced our ability to subdivide disease based on its genetic context.

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Hematological Malignancy: A Paradigm for Translational Cancer Medicine

In hematological malignancies, the refinement of disease diagnosis, based on the elucidation of specific molecular abnormalities, has impacted significantly on the development of targeted therapies. Thus, identification of the t(15;17) translocation in acute promyelocytic leukemia (APL) has predicated the development of a differentiation therapy employing All-Trans Retinoic Acid (ATRA) [1], while the anti-apoptotic *BCR-ABL* fusion protein provides a disease-specific target for tyrosine kinase inhibitors (TKI) as the new “standard of care” in Chronic Myeloid Leukemia (CML) [2]. In Diffuse large B-Cell Lymphoma (DLBCL), the redefinition of disease through

microarray profiling [3] has provided a rationale for the stratification of patients, based on their molecular subtype [4].

The evolution of TKI therapy in CML also highlights that “bench to bedside” is not a “one-way street;” precise real-time PCR (RQ-PCR) monitoring of CML patients receiving Glivec and DNA sequence

analysis revealed distinctive resistance mechanisms based on mutation of the kinase domain “pocket” [5]. This allowed scientists to go back to the bench to re-engineer second and third generation TKI molecules with greater flexibility, which could inhibit the fusion protein even in the presence of kinase domain mutations [6, 7].

Redefining Solid Tumors and Identifying Novel Therapeutic Targets

While molecular pathology and targeted therapy have demonstrated clear patient benefit in hematological malignancies, definition of genetic context and the application of ‘omics-based approaches are now significantly refining our understanding of solid tumors, with a corresponding up-scaling of precise disease stratification and molecularly guided therapeutic intervention modalities. In breast cancer, gene expression profiling has led to the development of molecular signature di-

agnostics such as MammaPrint and Oncotype Dx [8, 9], and their application in prospective clinical trials of selected patient groups has indicated their utility in (a) identifying patients at high risk of recurrence and (b) reducing adverse treatment effects in low recurrence risk patients [10]. In colon cancer, biomarker patient selection by K-Ras mutation screening has identified a subset of patients who can benefit from anti-EGFR therapies, with clear improvement in response rate identified in a number of clinical trials (CRYSTAL, OPUS [11, 12]). In malignant melanoma, identification of somatic mutations in the gene encoding the serine threonine kinase B-raf (BRAF) has permitted the development of mutant B-raf inhibitors such as PLX4032 (Vemurafenib), providing an effective oncogene-targeted therapy in this aggressive form of cancer [13]. Drugs like Vemurafenib herald the future explosion in novel therapies that are informed by cancer biology for the treatment of diverse malignancies.

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The Second Challenge: Embedding Our Redefined Cancer Biology in Cancer Care

The ability to interrogate a patient’s cancer genome using a variety of transformational technologies and recommend a specific treatment plan for that patient based on their own tumor’s biology will fundamentally refine our clinical paradigm for cancer care. Maximizing the benefit of a targeted treatment approach for those patients who will respond, while minimizing unnecessary side effects in nonresponders, has implications not only for improving cancer care and addressing quality of life issues, but also has potential for health economic benefit. This will require a significant change, however, in clinical practice, not only for the clinician and the patient, but also in how we define comprehensive cancer care. A broader definition of the clinical Multidisciplinary Team (MDT) needs to emerge, which embraces not only our traditional MDT disciplines but also involves new and evolving translational cancer medicine themes, including advanced molecular pathology/diagnostics, pharmacogenomics, real-time imaging, drug discovery/development, and bioinformatics/epidemiology. It is clear that not all institutions will have such critical mass, and specialist cancer centers must be encouraged and appropriately resourced to deliver this new clinical paradigm. Pathology must embrace and master the complex ‘omics technologies and associated bioinformatics challenges and provide validated companion diagnostics that will be crucial to the success of disease stratification and targeted therapeutic interventions.

Responding to the Challenge: Establishing a New Blueprint for Translational Cancer Medicine

The key challenge for cancer medicine globally is to step back and consider how to perform drug development and clinical

trials in the context of a redefined classification of cancer. Our current model is most likely not “fit for purpose.” We need to engage with all stakeholders and develop a new “Translational Cancer Medicine” paradigm that responds and adapts to the more complex 21st century view of cancer. Two recent discoveries highlight those opportunities but also the challenges that have to be faced in delivering this translational cancer medicine revolution. The recently published genetic and transcriptome analysis of almost 2,000 breast cancer primary tumor samples with long-term clinical follow-up by the METABRIC consortium [14] has revealed a new “biological road map” for breast cancer, which allows the disease to be classified into 10 molecular subtypes. While some subtypes are known (e.g., HER-2 gene cluster), the research also highlighted novel subtypes (e.g., “immune system genes cluster”). Combining systematic molecular interrogation of the tumor samples with precise clinical follow-up data allowed classification of each of the 10 clusters identified, based on their prognostic significance.

While the results of this study have significantly altered our understanding of breast cancer and provide relevant targets for diagnosis, prognosis, and therapy, in truth we may simply be at the crest of a “molecular wave.” In another study, presented at the recent AACR 2012 meeting in Orlando, researchers from Washington University School of Medicine and The Siteman Cancer Center performed “deep” sequencing of the genomes of 50 breast cancer patients and identified over 1,700 mutations, many of which were unique to each cancer patient, thus revealing the incredible diversity of this disease, which will presumably also be reflected in similar studies in other cancers. Given this biological complexity, how do we translate these results into real benefit for the cancer patient? The answer lies partially in the rich clinical annotation that accompanies these biologically interrogated samples—in this study the molecular data was generated from tumors of patients receiving aromatase inhibitors as part of a clinical trial. Optimal translation to the clinic will require an increasing number of novel adaptive clinical trial designs, linking genomic or proteomic alterations to relevant clinical parameters including treatment response and survival. This will enable more effective drug development and early implementation of clinical advances in treatment into clinical practice.

Conclusion

In conclusion, cancer research has entered one of the most exciting and challenging times in its recent history. In order to respond to this challenge, we must consider a new cancer medicine blueprint that engages and responds to all stakeholders. In this way, rapid advances will be ensured as a result of the unprecedented discoveries in cancer biology and an enhanced standard of care provided for the cancer patient, reflecting translational oncology in the 21st century.

This article is the first in a series in *European Perspectives* that will engage with the European Oncology community to identify the ways in which this aspiration for enhanced standard of care for the cancer patient can be realized.

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EDITOR'S NOTE: For additional insights into issues affecting oncology practice in Europe, please visit http://sto-online.org/european_perspectives for an interview of Patrick Johnston by Mark Lawler, as well as a roundtable discussion between Patrick Johnston, H.M. Pinedo, Pierfranco Conte, and Thierry Le Chevalier. We encourage your participation and welcome your comments.