Personalized Medicine: Does the Molecular Suit Fit?

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BESPOKE MEDICINE: MOVING AWAY FROM THE "ONE SIZE FITS ALL APPROACH"

The term "tailored therapy" has entered the lexicon of terms that we employ to describe stratified or personalized medicine approaches, whether it be in cancer or in other human diseases. Borrowing another phrase from the clothing industry, the idea that we can craft a "bespoke" therapy, underpinned by our knowledge of disease biology, conjures up a similar metaphor that reflects our ability to move away from the traditional "one size fits all" approach that has been the standard of care over the last 30 years. A crucial component of this bespoke therapy is the increasingly important role that genetic context plays in informing the clinical decision making process.

TRANSLATING BIOLOGY TO THERAPY: THE CHRONIC MYELOID LEUKEMIA PARADIGM

Initial successes were predicated on our ability to dissect out the key molecular instigators of hematological malignancies, with chronic myeloid leukemia (CML) representing an early paradigm for disease biology informing clinical application. The evolution of imatinib mesylate, a tyrosine kinase inhibitor (TKI), as a therapy for CML is, in essence, a history lesson in personalized medicine. The observation of the Philadelphia translocation by Nowell and Hungerford, the identification of the Abelson oncogene (ABL) as the key molecular partner by Janet Rowley, the demonstration by George Daley that BCR-ABL can cause leukemia in mice: these and many other key observations led Brian Druker, Nicholas Lydon, and Charles Sawyer to realize that employing a strategic approach to disrupt the key molecular function of BCR-ABL, its tyrosine kinase activity, could underpin a therapeutic intervention that is now the standard of care in this malignancy [1]. Recognizing their seminal achievement, Druker, Lydon, and Sawyer were joint recipients of the Lasker Prize in 2009.

TARGETED THERAPY IN SOLID TUMORS: THE IMPORTANCE OF GENETIC CONTEXT

Increasingly, the principles that were brought into clinical practice in hematological malignancies are now being applied with varying levels of success in solid tumors [2–4]. However, while the acquired genetic lesion in CML is present in essentially 100% of cases, the molecular landscape in solid tumors is

more complex. Initial excitement on the ability of approaches that target the epidermal growth factor receptor (EGFR) to achieve therapeutic efficacy in diseases such as lung or colon cancer was tempered by the realization that genetic context played a crucial role in determining this efficacy. Thus, in non-small cell lung cancer (NSCLC), the use of EGFR TKIs such as gefitinib or erlotinib is only effective in patients harboring EGFR-activating mutations. Initial studies indicated that these mutations were only present in 7%–10% of patients [5]. However, these figures were compiled from white patients. In Asian patients, for example, the incidence of EGFR mutations is more than 30%, reflected in a concomitantly higher response rate to anti-EGFR approaches [6]. Therefore, genetic context should not only be considered at the individual level, but also at the level of the population.

PERSONALIZED MEDICINE: THE CHALLENGE OF GENOMIC DIVERSITY

It is, thus, at the population level where we must focus more of our efforts. There is a conceptual difference in how we best utilize the promise of discovery biology and personalized medicine when compared with our more traditional approach. Rather than focusing on the diversity of the disease, the emphasis needs to shift to human genomic diversity and the concept of genetic context described above. The example of RAS mutational status predicting response to EGFR inhibitors in colorectal cancer [7] is increasingly being reflected in other malignancies, emphasizing our need to link new therapeutic innovation with diagnostic innovation and the provision (and reimbursement) of companion diagnostics.

Returning to CML, a recent study from Asia has indicated a new mechanism of resistance to imatinib mesylate and other TKI inhibitors. Researchers in Singapore used a parallel sequencing approach to identify an intronic 2903 base pair deletion polymorphism in the *Bim* gene in CML patients who are resistant to TKIs [8]. *Bim* is a member of the *bcl-2* gene family which regulates cell death. The deletion event leads to a fusion of exons 3 and 4 of the *Bim* gene, leading to a mutant protein that is unable to regulate cell death. Given that TKIs mediate their effects in CML through cell death pathways, this mutation underpins a new mechanism of resistance to TKI therapy. Evaluating the frequency of this mutation in over 2,500 normal individuals, the researchers revealed that this

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aberration is present in over 12% of individuals of East Asian origin, but is entirely absent from European or African populations.

Intriguingly, this molecular aberration is not confined to mediating resistance to TKI therapy in CML. The researchers also evaluated patients with lung cancer for this deletion and demonstrated both its presence and its role in mediating resistance to erlotinib in the lung cancer patient cohort [9], further emphasizing our need to focus on genetic, rather than disease diversity as we strive to realize the promise of personalized medicine. We need to develop a new roadmap that allows us to exploit our increased understanding of the malignant process, because the challenge lies not so much in defining disease biology, but in translating this biology at both the individual and population levels.

However, the potential of personalized cancer medicine is being tempered by a realization that many challenges remain, not least in the potential increased costs associated with targeted therapeutic approaches [10]. Importantly, we need to refine our current algorithm at all stages of the cancer clinical trial continuum, from drug discovery science through phase I development to clinical application. In Europe, the regulatory environment must also evolve, to ensure more effective clinical trial activity for the European cancer patient. The new Clinical Trials Directive [11] and proposals for new data protection [12] and biobanking [13] regulations need to be aligned with the realities of 21st century medicine; otherwise they will significantly limit cancer clinical trial and translational research activity in Europe.

REFERENCES

1. Druker BJ. Perspectives on the development of imatinib and the future of cancer research. *Nat Med* 2009;15:1149–1152.
2. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273–1283.
3. Lièvre A, Bachet JB, Le Corre D et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006;66:3992–3995.
4. Kwak EL, Bang YJ, Camidge DR et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693–1703.
5. Yang SH, Mechanic LE, Yang P et al. Mutations in the tyrosine kinase domain of the epidermal growth factor receptor in non-small cell lung cancer. *Clin Cancer Res* 2005;11:2106–2110.
6. Zhou W, Christiani DC. East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. *Chin J Cancer* 2011;30:287–292.
7. Shankaran V, Obel J, Benson AB 3rd. Predicting response to EGFR inhibitors in metastatic colorectal cancer: current practice and future directions. *The Oncologist* 2010;15:157–167.
8. Ng KP, Hillmer AM, Chuah CT et al. A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. *Nat Med* 2012;18:521–528.
9. Sullivan R, Peppercorn J, Sikora K et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–980.
10. Proposal for a Regulation of the European Parliament and of The Council on clinical trials on medicinal products for human use. Available at http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm#rlctd. Accessed May 9, 2013.
11. European Commission. Protection of personal data. Available at ec.europa.eu/justice/data-protection. Accessed May 9, 2013.
12. Biobanks for Europe: A challenge for governance. A report from the Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research. European Commission 2012. Available at http://www.coe.int/t/dg3/healthbioethic/Activities/10_Biobanks/biobanks_for_Europe.pdf. Accessed May 9, 2013.

EDITOR'S NOTE: Accompanying this article is an online video roundtable (http://sto-online.org/european_perspectives) in which the authors highlight the successes but emphasize the challenges that the oncology community faces in delivering on the promise of personalized medicine.

THE PERSONALIZED MEDICINE ROADMAP: MAXIMIZING THE ACADEMIA-INDUSTRY INTERSECT

Another crucial component in our personalized medicine roadmap is the need for new models of collaboration and co-operation. Academia can deliver on discovery science, not only in the laboratory, but also increasingly in the patient. The mantra of “bench to bedside and back again” is the cornerstone of modern translational medicine. However, the ability to deliver new drugs and therapies is a skill set, that in the main, even large academic institutions do not possess. Industry may be at a crossroads, particularly in the context of the patent cliff, but it still possesses the skills, expertise, and capacity to cross the rubicon and deliver a new class of effective medicines with their origins in excellent discovery science. The crucial requirement is to reposition the academia-industry intersect, such that our efforts are discovery science led, with all partners performing the tasks that they do best. This will be achieved through a level of innovation, expertise, and added-value collaboration in a timely fashion that has maximum impact for the most important component of the partnership, the cancer patient.

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