The Price of Hope: Personalized Medicine in 2014

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In 1994, shortly after taking my first faculty position, I was invited to give Medical Grand Rounds at my new institution. The title of my talk was “Novel Therapeutic Applications of Cancer Biology.” Today, the title would be “Personalized Medicine in Oncology.” My Kodachrome slides covered numerous biologically rational molecular targets and their proposed treatments, including RAS (farnesyl transferase inhibitors), MYC (retinoic acid—my own research interest at the time), P53 (gene therapy), BCL2 (antisense oligonucleotides), and growth factor receptors (receptor antagonists), only the last of which has proven to have any clinical utility. At that time, the notion of targeting cancer cells based on their molecular derangements was being evaluated mainly in preclinical studies and early-phase clinical trials.

Much has changed in the past 20 years. Today, most people don’t know what a Kodachrome slide is, and, more importantly, several molecularly targeted anticancer agents have demonstrated dramatic clinical activity in molecularly defined patient populations. The “poster child” for targeted therapy is imatinib, which has kept many patients with chronic myelogenous leukemia (CML) in remission for well over a decade. But most cancers are not as molecularly homogeneous as chronic-phase CML. The results achieved with targeted agents in solid tumors have been far more modest, because of widespread tumor cell heterogeneity and energetic exploitation of alternative growth and survival pathways leading to the relatively rapid emergence of resistance. Nonetheless, we have learned that defining patient subsets based on predictive biomarkers allows us to target specific treatments to those who will benefit most, while avoiding undue toxicity to those who will not benefit. In thoracic oncology, we are finally starting to understand how to use epidermal growth factor receptor (EGFR) inhibitors most effectively, thanks to the commitment of thousands of patients and many investigators who participated in relevant clinical trials over the past decade.

Being enticed by the marvels of molecular technology and the promise of personalized medicine is easy, particularly when confronted by the limitations of current therapy. I recently received an e-mail from the husband of a woman with advanced non-small cell lung cancer (NSCLC) harboring wild-type EGFR, ALK, and ROS1. The plaintive tone was all too familiar. He had done his online research and, to his credit, was turning to the science of molecular tumor profiling rather than to laetrile. For only \$40,000, the e-mail said, he could ensure that his wife would get “the best and most appropriate care.” For him, this was the price of hope.

But separating the hope from the hype is important, as is clarifying the line between research and clinical reality. A rapidly growing number of commercial vendors offer molecular tumor profiling services that purportedly guide personalized therapy. However, the number of predictive biomarkers and targeted therapies proven to benefit patients with solid tumors remains relatively small, a fact that is not clearly evident from current news stories or most oncology journals. The promise of personalized therapy is not yet commensurate with the hype it has generated. But our patients only hear the hype, from both the lay press and direct-to-consumer advertising. The FDA is to be applauded for the recent warning regarding the need to validate the benefits of direct-to-consumer testing. As academic oncologists, we could also present a more balanced reality when interacting with the press.

The impact of this hype extends beyond our patients. Many of the calls I receive from community oncologists reflect a growing confusion about the prevailing standard

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of care. These physicians tell me that, at every meeting, they are told they aren't practicing modern medicine if they don't routinely check for mutations of gene X, despite little evidence that drugs targeting gene X improve outcomes. A horde of commercial entities inform us that their molecular profiling services will lift our practice from the dark ages and enlighten us with the wisdom to provide the best possible care for our patients. However, these entities largely ignore the fact that the vast majority of biomarkers in these profiles have not been clinically validated.

Even NCCN can sometimes jump on the bandwagon. The updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC now recommend that, "EGFR ± ALK testing should be conducted as part of multiplex/next-generation sequencing."¹ The guidelines list potential targets beyond EGFR and ALK, along with "available" agents aimed at these targets, even though the activity of several of these agents in NSCLC is currently supported only by single-patient case reports. I am not an oncologic Luddite, but the wastebasket of oncologic history is strewn with rational strategies that didn't pan out when rigorously evaluated in prospective clinical trials.

That our increasing understanding of cancer biology offers great promise for turning cancer into a chronic disease through personalized therapy is not in doubt. But before getting everyone's hopes up and spending billions of dollars on nonvalidated biomarker assays and the treatments derived from them, we need to do the work to ensure that we are getting the right drug to the right patient. This does not mean we need to work out every detail of an agent's use before rolling it out, but it does mean we need to ensure the analytic and clinical validity of the test and to define specific populations in which the agents have significant clinical utility.

Currently, broad molecular profiling of cancer remains a research tool, which is best used to direct patients to ongoing clinical trials. "One-off" treatments based on isolated molecular findings are unlikely to benefit patients and will not advance the field. Rationally conceived "master protocols" are being developed by both academics and industry, which will direct patients into specific clinical trials based on the molecular profile of their tumor. Some such studies are already underway and should be supported through robust patient enrollment.

We have learned that the therapeutic relevance of putative biomarkers depends on their context. Thus, large registries are needed to capture the vast amounts of molecular and clinical data that will allow us to sort through the complexities of cancer biology. It is only through such rigorous efforts that we will ultimately justify the price of hope.

References

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