Personalized Cancer Care Is Not New

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The advent of rapid DNA sequencing technology and its application to cancer has shifted our understanding of the disease and the basis of its treatment. Tumors formerly categorized as a single entity on the basis of microscopic appearance are now known to be diverse in their molecular characteristics. Despite their clonal interrelationships, tumors within an individual have been shown to be heterogeneous in different sites and in large masses in the same site. And the presence of particular genetic lesions has been found sufficient to dictate the choice of therapy for a number of tumor types including subsets of lung cancers, melanomas, thyroid cancers, and others.

The application of these sophisticated analytic techniques to arrive at a therapy for a particular cancer has been called “personalized oncology.” However, we should not regard the creation of a particular treatment plan for an individual patient as a new idea. The image of oncology as applying routine treatment “recipes” to patients with particular types of cancer is not a full picture of the discipline. Indeed, the notion of tailoring the treatment to a patient’s particular tumor is as old as oncology itself.

In the late 1940s, once it became clear that certain drugs could cause regressions in patients with cancer but were also toxic to normal tissues, it became necessary to develop an approach to cancer treatment that gave the patient the best chance of response with the lowest risk of life-threatening toxicity. One of the pioneers in medical oncology and an original founder of the American Society of Clinical Oncology, Jane Cooke Wright, M.D., who died on February 19, 2013 at age 93, brought passion and persistence to her work as a physician and researcher. The rare responses that were seen with chemotherapy encouraged her to try to explain why some patients responded and others did not.

Wright analyzed the activity of anticancer agents by comparing tissue-culture response to patient response. Dr. Wright put fresh tumor biopsy material into tissue culture and assessed

whether an in vitro response to a particular agent predicted a clinical response in the patient to the same agent. In a *New England Journal of Medicine* paper published in 1957, she laid the groundwork for tailoring treatment to a particular patient’s tumor by reporting the correlation between the in vitro and in vivo response.

Tools to refine the choice of personalized therapy have continued to evolve. Despite the promise, no method of tailoring treatment to the particular drug sensitivities of a tumor in an individual patient based on pretreatment testing have become a standard for cancer management. Instead, the focus has been on identifying the presence of particular genetic lesions that predict for response to particular drugs. Tumors with mutations in driver kinases are more likely to respond to kinase inhibitors. Tumors with defects in the BRCA1 DNA repair machinery are more likely to respond to a DNA damaging agent plus a poly(ADP-ribose)polymerase (PARP) inhibitor. Tumors that express a particular target antigen are more likely to respond to antibodies, immunotoxins, or engineered cells that recognize that antigen. As we learn more about molecular mechanisms of resistance, it seems that combining inhibitors of sequential steps in a signaling pathway or blocking two pathways may improve response and decrease emergence of resistance.

Nearly all the work to personalize cancer treatments has been focused on defining characteristics of the tumor that predict for response to a particular treatment. This focus is too limited. Treatment plans must also take into consideration certain features of the patient. Pharmacogenomics may influence the metabolism of a drug with either enhanced or inhibited activity; for example, irinotecan is unsafe to give patients with Gilbert’s syndrome, an otherwise completely benign defect in uridine diphosphate glucuronyl transferase (UGT-1A), because the missing enzyme is crucial to detoxification of the drug. Cytochrome P450 enzyme 2D6 polymorphisms can affect the efficacy of narcotic analgesia.

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Functional assessment is also a component of personalized cancer care. A 75-year old patient with several serious comorbidities and Karnofsky performance status of 60 is unlikely to tolerate the same therapy as the 32-year-old healthy athlete with performance status of 100. Excellent oncology care has always been personalized, not only taking into account important features of the tumor and the physiology of the host, but also the holistic idea of the emotional and spiritual state and the goals of the patient.

The progress that is taking place based on exploitation of new knowledge of what makes cancers progress is leading to interventions with unprecedented levels of antitumor activity and resulting in a prolongation of survival of patients with tumor types that would have been rapidly fatal a few years ago. Yet our advances in the molecular nosology of cancer should not be thought of as a revolutionary change in the philosophy of the field. The implication that oncology care was “one size fits all” is incorrect. Oncologists have always sought to create treatment that was well-suited to the individual patient. There was a time when the state of the art in pathology was capable of recognizing three types of lymphoma. Tumors derived from T cells and tumors derived from B cells were treated similarly. As a consequence of advances in technology, first improved

microscopy, then improved cytogenetics, then monoclonal antibody-facilitated improvement in definition of cell surface characteristics, and most recently, sophisticated analyses of genes and their products, we now recognize that there are at least 50 kinds of lymphomas. And as a consequence of new therapeutic agents, particular regimens have been designed that are highly effective in patients who have the same molecularly-defined disease types. The implication of “personalized medicine” is a “one size fits one” paradigm. We are and should be a long way from that extreme.

We still treat entities that we recognize as being of a particular type with a treatment that has been shown to work in tumors of that type, as we should. The notion that this is a paradigm shift reflects a failure to understand oncology and the principles upon which the field was founded. The philosophy is the same; the knowledge base and the therapeutic tools are changing and we are just getting better at executing the strategy. Molecular nosology of cancer is not personalized oncology. Personalized oncology is much bigger than that.

DISCLOSURES

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