Peek Before You Treat? Is It a Fantasy or Reality?

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Only a couple of decades ago, researchers were focused on discovering new classes of cytotoxic agents to treat patients with cancer. In the clinics, the goal was to try new agents and new combinations in patients with various types of cancers. “Active” drugs were identified, and many were approved for use even if only a fraction (generally 15% to 20%) of patients had a responsive cancer. Most patients’ cancers were resistant, and each patient experienced considerable toxic effects. In other words, toxic effects were more or less guaranteed, but clinical benefits were not. This was and has been a source of significant frustration for everyone, but particularly for patients and their caregivers. This fundamental strategy of recommending the same therapy to a group of patients with similar cancer conditions (eg, stage IV lung cancer), called “empiricism,” has plagued us for decades. We now know that most cancers are highly complex and that even the same tumor type can harbor hundreds of different genetic abnormalities.¹ The number of somatic mutations in one breast cancer can be more than 1,000, and up to 100 of these can be unique compared with those of another breast cancer (of similar stage). Not all somatic mutations are considered as “activating” or driving the cancer. It is time we begin our journey to end the empirical approach.

What possible solutions are there? Solutions are not simple for a complex illness like cancer, but we can cite many examples of success of a rational approach to cancer treatment. Quick examples are imatinib for chronic myelogenous leukemia and trastuzumab for *ERBB2* protein–overexpressing breast cancers. How did we get here? We stand on the shoulders of many innovative and dedicated investigators who recognized years ago that administering the best guessed cytotoxic combination and then finding out whether it helped the patient (or not) is not the solution. As Daniel D. Von Hoff, MD, said in his David A. Karnofsky Memorial Award Lecture at the 2010 ASCO Annual Meeting, “We need new tools to measure sensitivity in a greater percentage of patients and need different approaches.” This thought process led to many innovations, including the development of a number of chemotherapy sensitivity and resistance assays (CSRAs) that were used to interrogate tumor explants (tumors removed from patients and tested under specified laboratory conditions). The concept of using CSRAs, which in retrospect appears pedestrian, formed the basis for what we might consider today’s advanced thinking. Essentially, tumors cells from patients were exposed to commonly used cytotoxic agents, and the behavior of the cells (number of colonies formed or the fraction of surviving cells) was assessed. Although early results were tantalizing and piqued the interest of many oncologists, media, and patients alike, the entire

enterprise has fallen short of our expectations of rigor in establishing high levels of evidence, and therefore none of the CSRAs is recommended for routine use. How did we reach this conclusion?

In 2004, ASCO published a technical assessment of CSRAs.² Recently, *Journal of Clinical Oncology* published an update, the ASCO Clinical Practice Guideline Update on the Use of Chemotherapy Sensitivity and Resistance Assays.³ The same clinical questions and inclusion and exclusion criteria that were used in the original guideline were used for this update (see the update Data Supplement at www.asco.org/guidelines/csra).

The Update Committee reviewed data published between December 1, 2003 and May 31, 2010. MEDLINE and the Cochrane Library were searched. The literature search yielded 1,298 articles for abstract review. Of these, only 21 met defined inclusion criteria and underwent full text review, and five⁴⁻⁸ were included for data extraction.

The 2011 recommendations remain the same as in the original guideline: “The use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient’s health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.”^{3(p3328)}

However, not all of these efforts have been in vain. We can say that we have clung to the concept of individualization of therapy envisioned by our predecessors and it has now deeply permeated our psyche. It is now the dominant force for innovation in cancer therapy. The current advances in biotechnology have thrust us into another orbit (solar system or galaxy). We have much greater understanding of cancer genetics, proteomics, and patient genetics. We no longer interrogate the whole cell, so to speak. Instead, we interrogate various components of the cells (microRNA, proteins, and genes). We now recognize that thriving cancer cells use a number of strategies to overcome stress or injury and that cancer cells have an immense repertoire of tools to bypass an injury, similar to the techniques used by microbes (bacteria and viruses). We also recognize that a single-driver genetic event is rare in most cancers. Most cancers have to use networks of multiple genes and proteins to proliferate (it can be likened to a gigantic opera but with a number of backup casts). But the vulnerable entry points of cancer cells are probably buried in these networks, and if we use specific strategies (Yervoy for melanoma, anti-BRAF for certain

melanomas, crizotinib for certain lung cancers), our patients can derive some benefit.

So what is the shape of things to come? We do not really know, but certainly it will not be the shape we are used to. With efforts like the Cancer Genome Atlas and the proteome catalog, we will have wealth of information to act on. The current drug discovery process is already a significant departure from procedures of the past. Many pharmaceutical companies and academic researchers have adopted smart drug discovery processes through which the drugs target specific molecular pathways and specific proteins (sometimes certain configuration of proteins). A gene-editing technique to treat disease has even made its debut.⁹ This approach will propel us to interrogate every patient's tumor (and genetics) before we recommend a therapy. It is quite possible that in the future, therapy will not necessarily be specific to a tumor type but will be directed against an immunologic pathway that is protecting cancer cells. We will play the same game as the cancers do; cancers overcome injury by developing novel mutations or by using alternate pathways, and we will be ready to recognize them and, we hope, inhibit the process with yet another specific agent. We can conceive that such a strategy, if successful, could make advanced cancer a chronic illness. Consider the context in which we live today, then imagine a scenario in which our patients will live on with cancer for a very long time.

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Finally, we celebrate the effort of the pioneers who brought us the CSRA's. Even though CSRA's have fallen out of use, these efforts have ushered in an era of rational therapy driven by a high level of fundamental knowledge of cancer. The end of the guessing game is in sight.

Accepted for publication on July 27, 2011.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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DOI: 10.1200/JOP.2011.000405

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