Precise vs Imprecise Medicine

This issue of *Clinical Advances in Hematology & Oncology* includes articles that demonstrate how two opposite approaches to cancer therapy can be correct. I believe that the future of cancer therapy will involve both.

In this era of personalized medicine, emphasis has been placed on identifying therapies that are tailored to individual patients and their tumors. The identification of molecular targets that are specific to a patient's tumors should maximize the response while minimizing the toxicities. We need to not dispense with the flip side, however: the "one therapy fits all" approach.

Without a doubt, personalized therapy for cancer patients based upon tumor mutations has transformed medicine. Although these changes have mostly affected our understanding of individual tumor behavior, they also have resulted in improved clinical outcomes. Personalized therapy has been made possible by advances in next-generation sequencing (NGS) that enable rapid, cost-effective, and accurate determinations of genetic changes in a tumor. In their review article, Drs Monica Avila and Funda Meric-Bernstam describe the general approach to using NGS for the management of cancer patients. It behooves all physicians to develop an understanding of NGS because it will be an important part of medicine going forward. NGS is a term that is used quite broadly, being used to refer to almost any DNA sequencing methodology after Sanger sequencing. Assembly of the first human genome sequence, which was completed in 2002, was accomplished primarily using Sanger sequencing technology. As described by Muzzey and colleagues in *Current Genetic Medicine Reports* in 2015, sequencing the human genome required 12 years and nearly $3 billion, meaning that the technology was not viable to scale up for clinical use.

Where does NGS testing belong in clinical medicine in 2019? We know that 50% of melanomas are *BRAF* V600E–mutated and therefore likely to respond to treatment with vemurafenib. Although the high prevalence of the mutation in melanoma justifies an assessment for its presence in tumor tissue by polymerase chain reaction, what about tumors that are driven by the *BRAF* V600E mutation at far lower frequencies? To scan these tumors for the *BRAF* V600E mutation would be low-yield and would miss other potential targets. Publishing in the *New England Journal of Medicine* in 2015, Hyman and colleagues investigated the efficacy of vemurafenib in *BRAF* V600E–mutated nonmelanoma cancer. In more than 50% of the malignancies, the incidence of the mutation was less than 5%. In *BRAF* V600E–mutated non–small cell lung cancer, the authors demonstrated an overall response rate to vemurafenib of 42%. NGS provides a methodology to rapidly screen a tumor for a large array of mutations.

On the other hand, an ever-growing array of novel agents target specific proteins that—although they did not cause the tumor and do not result from an alteration in the genetic sequence—play a key role in tumor survival. One example is the inhibition of Bruton's tyrosine kinase (BTK) by ibrutinib in chronic lymphocytic leukemia (CLL). Although genetic abnormalities in BTK do not play a role in promoting or propagating CLL, inhibition of BTK is highly efficacious. Therefore, although sequencing in patients with lung cancer provides information to predict responsiveness to different agents, sequencing in patients with CLL does not.

CLL can progress on ibrutinib, however. In an analysis of four studies in patients with treatment-naive and relapsed CLL treated with ibrutinib, Woyach and colleagues, publishing in the *Journal of Clinical Oncology* in 2017, reported a 19% rate of progression on ibrutinib at four years. Of these patients, 80% harbored a C481 mutation in BTK. Although the C481 mutation is identifiable at relapse, the next step in the treatment algorithm could be venetoclax, which is not impacted by the mutation. Ibrutinib followed by venetoclax at relapse represents the "one size fits all" approach that demonstrates excellent efficacy, as discussed in the interview with Dr John Seymour in this issue. What if these patients were first treated with concurrent ibrutinib and venetoclax? These two agents are synergistic in vitro and impair CLL cell adhesion to the lymph node microenvironment by inhibiting the B-cell receptor signaling pathway, increasing the sensitivity to BCL-2 inhibition. Preliminary results with this combination from the CAPTIVATE study are extremely promising, and are not dependent on any personalized tumor assessments.

Therefore, the "era of precision medicine," although a nice catchphrase, ignores many of the great advances we have been able to achieve in clinical medicine. Some tumor types do require individual analysis, whereas others do not. Although much work remains to be done, perhaps we should call this the "era of great medicine to come."

Sincerely,

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