Tumor Heterogeneity and Personalized Medicine

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In the past 10 years, the number of tools available to treat cancer has increased, as has our understanding of what makes some cancers tick. The standard old-time cancer treatments were largely predicated on attacking DNA, an approach fueled by the belief that tumor cells divide more rapidly than normal cells. However, with the notable exception of Burkitt’s lymphoma, only a small percentage of tumor cells in a patient are dividing at any given time. As we have learned more about DNA repair mechanisms and epigenetic alterations in cancers, DNA remains a viable target for new cancer therapies, but DNA is not the whole story.

More recently, newer therapies have been aimed at the abnormal biology of cancer cells, including signal transduction and protein turnover pathways. A growing number of tyrosine and serine–threonine kinase inhibitors and monoclonal antibodies targeting signaling receptors have been developed; such agents have been shown to have antitumor activity and have reached the pharmacy. Among the tumors that appear to be responsive to these agents are some types that have never shown any meaningful responses to systemic cancer chemotherapy, including lung cancers, hepatoma, renal-cell cancer, neuroendocrine tumors, melanoma, and others.

This modicum of success (since none of the new agents produce cures in advanced cancers, although curative combinations may yet emerge) has led to a certain level of overoptimism in the field. A new world has been anticipated in which patients will undergo a needle biopsy of a tumor in the outpatient clinic, and a little while later, an active treatment will be devised for each patient on the basis of the distinctive genetic characteristics of the tumor. The path to that new world is already being cleared, with several companies now marketing genetic tests that measure the genetic signature of a tumor, with the expectation that this signature will direct the choice of treatment and predict treatment outcome.

However, as Albert Einstein noted, “things should be made as simple as possible, but not simpler.”¹ A serious flaw in the imagined future of oncology is its underestimation of tumor heterogeneity — not just heterogeneity between tumors, which is a central feature of the new image of personalized medicine, but heterogeneity within an individual tumor.

In this issue of the Journal, Gerlinger and colleagues² map out the remarkable heterogeneity within a single tumor. They obtained tumor samples from four patients with renal-cell cancer before and after treatment and took multiple samples from each patient’s primary and metastatic tumor sites. About two thirds of the mutations that were found in single biopsies were not uniformly detectable throughout all the sampled regions of the same patient’s tumor. A “favorable prognosis” gene profile and an “unfavorable prognosis” gene profile were expressed in different regions of the same tumor. Thus, a single tumor biopsy, the standard of tumor diagnosis and the cornerstone of personalized-medicine decisions, cannot be considered representative of the landscape of genomic abnormalities in a tumor.

Although intratumor heterogeneity is not a new idea, previous studies mainly involved next-generation sequencing of a single index lesion per patient and targeted sequencing of the mutated genes in other sites. Thus, those studies could not be used to identify branching evolution. This study uses unbiased whole-exome sequencing of multiple tumor sites in several different patients, with independent sequencing and
validation that the mutant genes are expressed and have altered function. On top of this, the authors show widespread alterations in the total number of chromosomes in the tumor cells (aneuploidy) and detect many allelic imbalances at the chromosome level, in which one allele of a gene pair is lost. These imbalances can be due to chromosome loss or gene imprinting and may alter gene expression.

Another key finding is that different regions of the tumor have different mutations in the very same genes (so-called convergent evolution), including in SETD2, PTEN, and KDM5C, which underscores the importance of changing particular tumor-cell functions as the tumor expands and evolves. From the function of the genes that were targeted for different mutations, it would appear that alterations in epigenetic mechanisms and signal transduction as the tumor evolves are keys to the tumor’s survival.

The news for personalized-medicine advocates is not all bad. The findings confirm that the genetic lesions that are found in the original tumor cells, the trunk of the evolutionary tree, are consistently expressed (e.g., the von Hippel–Lindau gene in renal-cell cancer). In addition, given that the tumor will do whatever is necessary to activate certain genes and inactivate others, the genes that are affected by convergent evolution may be suitable targets for functional inhibition or restoration. However, the simple view of directing therapy on the basis of genetic tumor markers is probably too simple.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.


Discontinuing Donepezil or Starting Memantine for Alzheimer’s Disease
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Donepezil, the most frequently prescribed cholinesterase inhibitor for the treatment of Alzheimer’s disease, was marketed in 1997 on the basis of the results of 3-month and 6-month clinical trials showing that patients had improvements in cognitive test scores and in the ability to perform daily activities, and subsequent trials indicated that the drug had efficacy over the course of 1 to 2 years. About half of the patients who are prescribed cholinesterase inhibitors, however, discontinue them within a year, apparently because of a perceived lack of efficacy and adverse effects such as anorexia, weight loss, agitation, bradycardia, and syncope.

Cholinesterase inhibitors do not appear to mitigate the deteriorating clinical course of Alzheimer’s disease, and as patients continue to worsen, it is difficult to determine whether they are benefiting from them. Treatment guidelines, however, recommend continuing cholinesterase inhibitors only when they are thought to be having a worthwhile effect.

In the United Kingdom, where decisions about medication coverage are made by the National Health Service (NHS), physicians have three guidelines-based choices when their patients who are being treated with donepezil reach a moderately severe level of cognitive impairment and it is uncertain whether the drug is helping or harming: continue donepezil, discontinue it, or switch to memantine, an N-methyl-D-aspartate-receptor antagonist that is specifically indicated for the treatment of moderate-to-severe Alzheimer’s disease in both the United Kingdom and the United States. The NHS does not approve the addition of memantine to a cholinesterase inhibitor. In contrast, U.S. physicians typically add memantine to ongoing donepezil treatment, frequently when patients are still mildly impaired, without waiting for their condition to worsen to moderate-to-severe (the indication for which the drug is approved by the Food and Drug Administration [FDA]).

The randomized, placebo-controlled Donepezil and Memantine in Moderate to Severe Alzheimer’s Disease trial (DOMINO; Current Controlled Trials number, ISRCTN49545035), reported by Howard et al. in this issue of the Journal, enrolled patients in the United Kingdom who had moderate-to-severe Alzheimer’s disease and who had been