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Recasting cancer trials

Wanted: faster, more effective ways of testing experimental cancer drugs for both single-agent and combination treatments.

Despite oncology pipelines being the richest in the industry, failures to translate successful phase 2 studies into phase 3 successes underline the need for greater innovation in the design and practice of cancer trials. Last month, the US Food and Drug Administration (FDA) issued draft guidance for its accelerated approval program, proposing that patients with highly aggressive breast cancers be eligible to receive novel experimental therapies for a few months. Permitting treatment-naive patients to receive experimental therapy first-line is a radical departure from conventional first-in-human studies, which have always tested new treatments in patients with advanced or metastatic disease that has failed to respond to available treatment options. As such, this initiative from the FDA is a welcome change that may facilitate the identification of cancer treatments with the potential to prolong survival for patient groups poorly served by existing therapies.

This issue of *Nature Biotechnology* surveys some of the most promising technologies currently being developed to interrogate cancer biology. They range from single-cell analysis approaches and genetically engineered mouse models to areas of new target discovery and experimental treatment modalities, such as oncolytic viruses. Deep sequencing and cancer genomics are broadening our understanding of the key genetic and epigenetic events in tumor initiation, progression and metastasis. Genome-wide studies are beginning to reveal unprecedented genetic and epigenetic heterogeneity within individual cancers, including population diversity in mutations involving putative driver loci. With these rapid advances in technology and our understanding of cancer genetics and biology, it is thus striking just how pedestrian progress remains in the clinic.

Today, setting up a cancer trial can take anywhere from six months to two years. By the time the trial commences, the agents being tested can already be outmoded—for example, many of the oncolytic viruses currently in human testing are using older generation constructs. One reason why cancer trials take such a long to time to get up and running is patient recruitment. Although an estimated 20% of adult cancer patients are medically eligible to participate in a clinical trial, concerns over quality-of-life issues and insurance reimbursement mean that accrual rates remain at the staggeringly low level of ~3%—and these rates are even lower for minorities and young adult cancer patients with high mortality rates.

As the standard of care improves for a cancer, the threshold for proving efficacy also rises making it more difficult to prove a new drug will extend patient survival. Regulators, in some cases, do consider alternatives to the gold-standard endpoint of overall survival, which requires conducting a trial for sufficient time to demonstrate a percentage of study subjects have survived for a defined period of time. Pfizer's Xalkori (crizotinib), for example, was approved for metastatic lung cancer based on an assessment of the proportion of patients with a predefined amount of tumor shrinkage over a time period. And sometimes, even if a single agent can successfully navigate the approval process and show statistically significant improvement in overall survival, the clinical benefit is often equivocal. Equivocation can also be attributed, in part, to the high level of 'me too' development that takes place in oncology drug programs.

Most cancer drugs are administered as part of a combination regimen (usually a cytotoxic chemotherapy paired with a molecularly targeted agent), and until recently, most new experimental therapies were tested either alone or in combination with approved drugs. Going forward, regulatory and corporate structures will need to move toward combinations of completely novel agents as first-line treatments to address the challenges manifest from our increasing understanding of cancer biology and heterogeneity. One such example is the finding that the complexity and redundancy of a tumor's dysregulated cellular regulatory pathways promote the emergence of resistant cells under the selective pressure of whatever cancer drug is being administered. New findings on the heterogeneity and evolution of tumors may increase the gap between the latest understanding of tumor biology and innovation in clinical trial design.

Of course, there is also the question of how to systematically determine the best combination of drugs for a particular cancer type—and ultimately the individual patient—in the first place. Until now, most combinations have been intuited from molecular knowledge of a particular cancer and suppositions that the different drugs address mutually exclusive pathways. But with molecular and biomarker information in hand, knowledge-based evolutionary and system-based models (p. 679) are likely to provide an even more rational choice of drugs for use in cocktails.

The final question that arises is how to determine the correct dosage of each component in a combination. The answer most likely lies in the use of adaptive trial designs, which allow researchers to make adjustments to dosage in response to data that are captured during the trial (p. 596). The I-SPY trials for invasive breast cancer and the BATTLE trial for lung cancer currently underway are good examples of how this works.

Thus, the central question facing clinical oncology is how to prioritize combinations to test when the number of patients for trials is so limited. Until now, we have just scratched the surface in terms of cocktails. Certainly, the science is arriving to identify the most promising combinations of molecularly targeted therapies. But the concern is that cultural issues, intellectual property concerns, litigation threats, red tape at institutional review boards and the lack of clarity at the FDA will mean that testing of combination therapies will take even longer than trials do now. That does not bode well for patient recruitment. Because if there is one thing that most cancer patients don't have, it is time.