Selecting Therapies for Cancer Patients: Past, Present, and Future

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We are in the middle of a revolution in DNA sequencing, which has ushered in the era of precision medicine in cancer. Unfortunately, the impact of precision medicine has been quite limited, reaching only about 15% of cancer patients, and benefitting only about 6% (SCIENCE, April 27, 2018, Volume 360, Issue 6387). An analysis of how therapies are selected for cancer patients helps explain the current challenges of precision medicine and points to a promising future for personalizing cancer therapies.

THE PAST: POPULATION MEDICINE

Since the inception of the modern FDA in 1938, drug development companies have followed a rigorous procedure for achieving FDA approval for new cancer drugs. They have selected groups of patients with similar cancers (such as breast cancer or lung cancer) and conducted "randomized controlled trials" (RCTs) that provided clear clinical evidence of the safety and efficacy of their drugs for the chosen groups of patients. Once approved, these drugs were given to new cancer patients with the same cancers as the patients in the RCTs.

THE PRESENT: PRECISION MEDICINE

The revolution in DNA sequencing, which started in the late 1990s, ushered in the era of precision medicine. The purpose of precision medicine is to develop cancer drugs that target DNA mutations present in cancer cells but absent in normal cells, thereby killing the cancer without harming the patient. These drugs are known as "targeted therapies."

Developers of targeted therapies were required to follow the same rigorous procedure for achieving FDA approval as the previous generation of non-targeted therapies. They selected groups of patients with similar cancer gene mutations (such BRAF or EGFR gene mutations) and conducted randomized controlled trials that provided clear clinical evidence of the safety and efficacy of their targeted drugs for the chosen groups of patients.

Once approved, these drugs were given to new cancer patients with the same cancer gene mutations as the patients in the RCTs.

Using this methodology, the FDA has approved 84 targeted cancer drugs over the past two decades. One of these drugs, Gleevec (also called imatinib), has worked miraculously for chronic myeloid leukemia patients who have a certain gene mutation ("BCR-ABL"). But to the surprise and disappointment of the precision medicine community, almost all other targeted therapies share two characteristics:

1. Like the earlier generation of non-targeted therapies, they work for only a minority of cancer patients, even though these patients have the mutations that the therapies target. Furthermore, drugs that initially work typically stop working after a relatively short period of time, ranging from a few months to a few years.
2. Most targeted therapies occasionally work for patients who do NOT have the targeted mutation. There is clearly something we do not understand about how these targeted therapies work.

The cancer community initially named this approach to developing targeted therapies "personalized medicine," but came to realize that grouping patients by cancer gene mutations was not personalized, it was simply a better form of population medicine that more precisely targeted populations of patients who shared one genetic characteristic. This approach was aptly renamed "precision medicine."

In addition to enabling the development of targeted therapies, the revolution in DNA sequencing led to a new discovery that explains much of the

disappointing similarity in the effectiveness of the earlier non-targeted therapies and the new targeted therapies - **cancers are heterogeneous**.

If you have cancer, you probably do not have one type of cancer. You most likely have five or more genetically distinct cancers (see Gerlinger et al. N Engl J Med. 2012; 366, 883–892 and Lohr JG, et al. *Cancer Cell*. 2014 Jan 13;25(1):91-101). This explains why a single therapy -- targeted or not -- typically fails to eradicate a patient's cancer. It very well may wipe out one of the five or more cancers, which then leaves room for the other cancers to grow.

If each cancer patient has a unique mixture of multiple different cancers, and that mixture is changing over time and in response to selective pressures from therapies that are effective against some but not all of the different cancers, how can we develop effective personalized therapies for each cancer patient?

THE FUTURE: PERSONALIZED MEDICINE

There are two emerging paradigms for developing personalized therapies for each cancer patient. The first modifies each patients T-cells (their cancer-killing immune cells) to target their unique cancers. These "immunotherapies" have achieved some spectacular early results (reminiscent of Gleevec in the early years of targeted therapies), but have encountered major barriers to widespread adoption, including extreme toxicity and prohibitively high costs of creating a custom therapy for each patient.

The second emerging paradigm of personized medicine for cancer uses a very old and low-tech method to find a combination of therapies that target each of the multiple types of cancers in each patient – **trial and error**.

Of course, trying the dozens of targeted therapies and hundreds of non-targeted therapies in each patient is not practical: the drugs are far too toxic, it would take much too long (decades) to try them all, and it would be prohibitively expensive.

The solution is instead to try the drugs OUTSIDE the patient rather than INSIDE the patient. That is, remove some of the cancer cells from the patient and and apply the drugs to these removed ("ex vivo") cancer cells. We can then try hundreds of drugs (in very small quantities) against hundreds of small collections of cancer cells. This approach (known as "functional testing") could identify effective cancer drugs and drug combinations for patients with no biomarkers, without imposing any toxicity during the testing process.

Cancer researchers have tried and failed for many years to create a reliable ex vivo cancer drug effectiveness test. Fortunately, recent advances in live-cell laboratory procedures and measurement tools have made this *ex vivo* trial and error approach possible.

THE TRAVERA APPROACH

Travera is pioneering a new approach to functional testing that offers the promise of identifying the personalized combination of drugs that will target each patient's uniquely heterogeneous cancer. The test is based on a new invention made at the Massachusetts Institute of Technology (MIT) and a new discovery made in partnership with the Dana Farber Cancer Institute (DFCI).

The new invention is a micro-electromechanical (MEMS) device that can weigh individual cancer cells with exquisite accuracy. This device, called the Suspended Microchannel Resonator (SMR), flows cancer cells through a tiny cantilever (a diving board containing a fluidics channel) and measures the change of the resonant frequency of the cantilever with a precision of one part in a billion. This precise frequency measurement enables us to calculate the weight of the cancer cells with sub-picogram accuracy.

The new discovery is that when cancer cells are exposed to effective cancer drugs *ex vivo*, they lose a tiny amount of weight very quickly, within a few hours, as they start the process of dying (apoptosis). Without artificial support, most cancer cells die naturally within 1 to 2 days of being removed from the human body, so speed is critical to distinguish between natural cell death and cell death induced by a cancer drug. The exquisite sensitivity of the SMR enables us to detect a cancer cell's response to a cancer drug while it is still a viable cell.

By measuring weight change rather than genomic biomarkers, Travera's testing approach effectively incorporates all genomic and proteomic biomarkers, both known and unknown, as well as a myriad of other known and unknown factors including epigenetic, metagenetic, environmental, and other factors that affect a cancer cell's response to a cancer drug. The weight change of ex vivo cancer cells in response to cancer drugs may become a "universal biomarker," shared by virtually all cancer patients, and applicable to virtually all cancer drugs.

Travera is currently developing a Laboratory-Developed Test (LDT) for clinically testing multiple FDA-approved cancer drugs against each patient's cancer cells. The test is initially being developed for the drugs that directly kill cancer cells, which represents a large majority of the cancer drugs in clinical use today. We are also developing methods for testing drugs that induce T-cell mediated cell death, starting with daratubumab.

The test will initially be available for multiple myeloma patients, followed by tests for breast cancer patients, non-small cell lung cancer (NSCLC) patients, and then other cancers to be determined in the future.

In addition to the universal nature of this test, the Travera approach has two particularly attractive clinical characteristics:

1. As it uses a single-cell measurement technology, it requires only a few thousand cancer cells for each drug tested. We are developing methods for replacing surgical resections and core needle biopsies (which yield millions of cancer cells) with fine-needle aspirates (which yield many fewer cells but are much less invasive to the patient), thereby dramatically reducing the health risks associated with biopsies.

2. The SMR is so sensitive that we can measure drug response in a single day. Instead of having to wait weeks for test results, patients and oncologists can find out which drugs are most likely to be effective within two days (assuming shipping the patient sample to our lab requires one of those two days).

This new approach to ex vivo trial-and-error drug testing, combined with a safe needle biopsy procedure, may enable a new strategy for combating heterogeneous cancers that change over time. Upon recurrence of a cancer, a patient could be retested against a large panel of candidate drugs to identify a new set of drugs that will be effective against their new heterogeneous mix of cancer cells. While this approach may not cure the patient of cancer, it could reduce a currently fatal cancer to a long-term chronic disease.

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