PERSPECTIVE

The precision–oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

Precision oncology promises to pair individuals with cancer with drugs that target the specific mutations in their tumour, in the hope of producing long-lasting remission and extending their survival. The basic idea is to use genetic testing to link patients with the drugs that will work best for them, irrespective of the tissue of origin of their tumour. Enthusiasm has been fuelled by reports of exceptional or super responders — individuals for whom experimental therapies seem to work spectacularly well.

In one such example, an individual with metastatic bladder cancer showed a dramatic response to the drug everolimus[1]. Sequencing later revealed that the patient had a mutation that affects the mTOR pathway, which is the mechanism of action of everolimus. Yet despite the hype surrounding rare cases such as these, most people with cancer do not benefit from the precision strategy, nor has this approach been shown to improve outcomes in controlled studies. Precision oncology remains a hypothesis in need of verification.

Few patients benefit from precision oncology. Data from some 2,600 people enrolled in a sequencing programme at the MD Anderson Cancer Center in Houston, Texas, showed that just 6.4% were paired with a targeted drug for identified mutations[2]. Similarly, the Molecular Analysis for Therapy Choice (NCI-MATCH) trial at the US National Cancer Institute has enrolled 795 people who have relapsed solid tumours and lymphoma, but as of May 2016 it had only been able to pair 2% of patients with a targeted therapy[3].

NOT SO EXCEPTIONAL

But being assigned such a therapy is not proof of benefit. When patients with diverse, relapsed cancers are given drugs based on biological markers, only around 30% respond at all, and the median progression-free survival is just 5.7 months[4]. Multiplying the percentage of patients receiving targeted therapies by this response rate, I estimate that precision oncology will benefit around 1.5% of patients with relapsed and refractory solid tumours.

It is on this tiny proportion of patients that the hopes for precision oncology have been built. Although many patients have undergone sequencing in the past decade (Foundation Medicine, a commercial provider of tumour profiling, has sequenced at least 18,000 patients), the number of reported cases of exceptional and super responders over that time are few. In a search of the biomedical literature with a colleague, we identified only 32 cases[5].

Moreover, even when vignettes such as these are reported, they often have major gaps. The number and duration of responses to previous therapies, and the number of patients who were treated to identify the super responder[5], are often omitted. Because even the most serious malignancies, such as pancreatic cancer, exist along a continuum, some patients are already destined to outlive the average. Indeed, we found several cases in which the 'exceptional' responders had already experienced exceptional responses to conventional chemotherapy before their supposedly miraculous response to precision oncology[5]. It is hard to avoid the unsettling conclusion that such cases do not reflect the success of precision oncology, but rather the selective reporting of individuals who were always likely to do well.

When considered objectively, the prospects and potential of precision oncology are sobering. At best, we may expect short-lived responses in a tiny fraction of patients, with the inevitable toxicity of targeted therapies and inflated cost that this approach guarantees.

PRECISION ONCOLOGY ON TRIAL

In medical science, the ultimate judge of a therapeutic strategy is the randomized controlled trial. So far, precision oncology has been tested in only one such published study[6]. The SHIVA trial assigned 99 patients with cancer to therapies based on an identified mutation or mutations, and 96 patients to the treatment selected by their physicians. Median progression-free survival, the primary endpoint, was almost equally poor in both cases (2.3 and 2.0 months, respectively).

No single trial can prove that a therapy does not work in any circumstances, and SHIVA is no exception. It paired patients with drugs for 'pathway' mutations, not just for mutations that can be targeted with drugs, allowing those running the trial to enrol more than a quarter of screened patients. But further randomized controlled trials are needed to test alternative hypotheses, and the use of different medications and alternative pathways. These trials will have to balance applicability and generalizability (the percentage of screened patients that can be enrolled) against the strength of the biological rationale. Several more trials are needed before we can judge whether this strategy is viable.

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Precision oncology is inspirational. What doctor or patient would not want to harness genetics to tailor a therapy to an individual? But travelling back in a time machine is also inspirational. Who would not want to wind back the clock to remove their cancer before it spreads? In both cases, however, as of 2016, the proposal is neither feasible, cost-effective nor assured of future success. Yet in only one of these cases does the rhetoric so far outpace the reality that we risk fooling even ourselves. ■

Vinay Prasad *is a haematologist–oncologist at the Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon, USA.*
e-mail: prasad@ohsu.edu

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