Precision or imprecision medicine?

“At the end of the day, we need to translate trial results into therapeutic decisions for our patients”

The term ‘precision medicine’ is abundant in the medical literature. But, what do we understand by this term? In clinical oncology, an accepted definition of precision medicine refers to therapeutic decisions guided by the molecular or genomic features of a tumour rather than on the basis of clinicopathological features. On closer examination, however, one wonders whether what we’ve unleashed is imprecision medicine. The SHIVA trial, for example, was received with both enthusiasm and disdain by the clinical community. The key conclusion from this prospective randomized study was that, for patients with solid tumours who had received several lines of treatment, no progression-free survival (PFS) benefit was derived from molecularly targeted therapies compared with physician’s choice of conventional therapy. Are these results bad news for those who expected precision medicine to become an instant solution to cancer management? In this issue, Le Tourneau and Kurzrock discuss this question 1 year after the publication of the trial results from SHIVA. The authors clarify one important consideration when interpreting the negative results of this study: SHIVA was an algorithm-testing trial. In other words, it was powered to determine whether the use of an algorithm-based approach to treatment allocation can improve patient outcomes — regardless of the nature of such allocated treatments.

An interesting feature of the SHIVA trial was that each patient served as his or her own control in terms of primary end point assessment. For those patients who crossed over from a therapy of physician’s choice to a molecularly matched therapy, outcomes were determined by evaluating the ratio of PFS duration observed with the latter to PFS duration observed on prior therapy. What the trial did not fully assess is whether the PFS ratio changed as a result of patients receiving selected therapy irrespective of the treatment allocation approach. This PFS ratio assessment is as pertinent to a traditional trial and not unique to precision medicine.

A crucial lesson that must be learned from SHIVA and other precision medicine trials is that the devil is in the detail, namely in trial design. In the precision medicine era, we are witnessing a rapidly changing environment in clinical research, where designs that made sense a few years ago are less pertinent today. How do we decide which end points are clinically meaningful, irrespective of how treatment is allocated? An inherent problem in assessing any clinical trial data is how to compare the often inconclusive results from separate studies with similar treatments and trial designs. If the

results of an algorithm-testing trial indicate that no differences in outcomes exist and, if this is what is being tested rather than the efficacy of a specific drug, one has to ponder the true premise of the trial. At the end of the day, we need to translate trial results into therapeutic decisions for our patients. Sound trial design also begins with a rational definition of trial arms and the expectations of what the trial is aiming to achieve. When assigning patients to treatment groups, what is ethically appropriate? Any potential risk derived from testing a therapeutic approach needs to be taken into consideration — is that always the case?

What might constitute an ideal precision medicine clinical trial? Several multicentre trials are currently being conducted to test different agents simultaneously using an efficient design strategy. NCI-MATCH is perhaps the most popular example among them. Thus far, 2,500 patients in the USA have been enrolled in one of the 24 arms of this trial, representing one-half of the recruitment goal. In 2013, 14 million people were estimated to have cancer in the USA. Obviously, the vast majority of patients will not be able to participate in or have access to the latest innovations. In precision medicine, some patients might not be treated with a life-saving treatment because molecular stratification denies them the opportunity to receive certain therapies, despite so-called equipoise. If the resulting data are poor or misinterpreted in light of the trial question, then this approach risks throwing the baby out with the bathwater, since trial data must inform clinical practice. The situation is worrisome because an increasing number of published studies periodically remind us of the differences in the access to cancer care and cancer medicines around the world.

To summarize, precision medicine can be considered more as imprecision medicine in light of its limitations; let’s not forget that, currently, this approach is only available to a fraction of patients with cancer worldwide. At least one in three of us can expect a cancer diagnosis in our lifetime and thus, for any of us who might receive such news in the near future, how will the perceived success (or failure) of precision trials affect the conversation with our oncologist? The outcomes for the great majority of patients with cancer in the near future rely heavily on the availability of good screening, diagnosis, radiotherapy and surgery services irrespective of precision medicine. Let’s not put all our eggs in one basket (trial) and, instead, face the situation as it is now, mindful of the implications for the future.

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Competing interests
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