COMMENTARY

Giving Up on Precision Oncology? Not So Fast!

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INTRODUCTION

The vision of matching the right patient to the right treatment at the right time has always been the Holy Grail of oncology. Until recently, very few cancer patients enjoyed the benefits of truly "personalized" a.k.a. precision therapy. With the exploding knowledge of tumor genotype, as well as increasingly available targeted treatment options, it seems that the era of precision cancer medicine is nigh. However, as with many new paradigms, there has been substantial pushback.

COMMENTARY

Precision medicine and precision cancer medicine, in particular, have been getting a great deal of attention recently. The vision is that matching the right patient to the right treatment at the right time will lead to improved outcomes, fewer futile treatments, minimization of toxicity, and perhaps an economic benefit to society. This vision is currently being carried out primarily through next-generation sequencing (NGS) panel testing of tumor tissue. Briefly, these panels consist of exon sequencing of a select number of genes associated with cancer, ranging from 30 to more than 500, as well as limited intronic sequencing to detect certain translocations or other structural variants. Many panels are carried out by specialized third-party laboratories, whereas some larger academic centers also perform in-house testing. As with many new ideas, a backlash was inevitable. Two recent editorials, one in *Nature*: "Perspective: The precision-oncology illusion,"[1] and one in the *New England Journal of Medicine*: "Limits to personalized cancer medicine,"[2] have presented a sobering and pessimistic view of the possibilities of using NGS mutation data to guide treatment decisions. Several themes that emerge in these editorials are: i) the clinical usefulness of targeted therapies is in doubt; ii) testing cancers with NGS panels has a very low yield for "actionable" mutations; and iii) the one published randomized trial of molecularly directed therapy, SHIVA,[3] did not show any advantage for genome-directed treatment. While both of these pieces are fundamentally correct that all new scientific hypotheses must fail to be falsified before being generally accepted, the editorials are misleading on several fronts.

First and foremost, precision oncology is being used in the clinic now. Genome-selected therapies such as vemurafenib for BRAF p.V600E-mutated melanoma, and crizotinib for ALK-rearranged non-small cell lung cancer, have definitive advantages in randomized-controlled trials of appropriately selected patients. These and quite a few other targeted small molecules are now a part of the standard clinical armamentarium and are recommended by trustworthy guidelines, such as those issued by the National Comprehensive Cancer Network (NCCN). The US Food and Drug Administration has also increasingly recognized this fact, and now routinely mentions that patients should have undergone treatment with a genome-directed therapy, if available, on antineoplastic drug approval labels.

Second, the editorials point out that enrollment on genome-directed "basket trials" has been very low, as a proportion of patients screened. One of these trials, performed at the MD Anderson Cancer Center, enrolled 11% of NGS panel-screened patients on genotype-matched trials, a number generally considered to be rather low. However, the patient population in this trial was drawn from gastrointestinal and breast cancer clinics, and the authors state "Notably, patients with diseases for which multiplex genomic testing is accepted as standard of care (e.g., lung cancer) were often tested without protocol enrollment and are under-represented."[4] Another well-known basket trial, NCI-MATCH, had an initial NGS-panel screening rate of 9% and an accrual rate of 2% (that is, ~1 in 50 patients ultimately enrolled in the trial). Importantly, the initial screening rate was close to the *a priori* estimated 10% rate.[5] Many other factors, e.g., patient and managing provider preference, play a role in the observed accrual of 2%. Unfortunately, progression of late-stage cancer while awaiting entry into a basket trial is not an uncommon reason for the lack of accrual. It is also important to note that the pace at which genomically targeted treatments are available (approved or investigational) is such that many of these low accrual rates are already out of date. When the NCI-MATCH trial opened in 2015, there were 10 arms; as of May 2016, there are 24. This reflects the pace at which genomic targets are being recognized and treatments are being developed.

Next, a brief word about the SHIVA trial, which is to date the only published randomized trial that compared genome-selected treatments to the standard of care.[3] This was a negative trial, which means that the study arm failed to demonstrate statistical superiority, as compared with the control arm. SHIVA used 11 possible treatments in the genome-selected arm, of which 7 were small molecule inhibitors. In contrast, there are now at least 68 cancer-targeting kinase inhibitors that are US Food and Drug

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Administration-approved or in advanced phases of investigation.[6] SHIVA also enrolled patients who "needed to have progressed on all molecularly targeted agents approved for their disease," reminding us that precision oncology is already in the clinic. By design, the trial was statistically powered to detect a 15% change in the rate of progression or death with the anticipation that the average patient enrolled would live for 6 months. Unfortunately, the actual average (median) survival in both arms of the trial was only 2 months, which was also the approximate length of time from the start of treatment to the first assessment for response (8 weeks). Randomized trials are negative for two major reasons: the new treatment is truly no better than the old treatment, or the trial is statistically underpowered. With the error in survival prediction, the SHIVA trial was most likely underpowered, meaning that the hypothesis that genome-directed therapy is better than the standard approach has not yet been disproven.

In the near future, the greatest challenge for precision cancer medicine will be twofold: i) matching the "most critical" genomic alteration with the "best available" drug; and ii) designing and implementing rational drug combinations. Kinase inhibitors in particular have varying substrate binding affinities, with resultant variation in "on-target" and "off-target" effects. Relatedly, it must also be acknowledged that the rates of treatment discontinuation for toxicity are substantial even with the so-called "targeted" drugs; e.g., a recent abstract presented at the 2016 American Society of Hematology conference reported that the most common reason for discontinuation of the BTK inhibitor ibrutinib was toxicity.[7] Recently, Dong *et al.* introduced a statistical framework for inferring driver variants and prioritizing drugs on an individualized basis[8]; such tools are likely to become increasingly available in short order. The problem of finding effective and tolerable drug combinations is more significant, and will require innovative solutions.[9]

In conclusion, I fully agree with the fact that new treatment approaches need to be rigorously tested for scientific validity. This is notwithstanding recent concerns that have been raised about discordance between NGS platforms,[10] which will need to be addressed. Clearly, clinical factors such as performance status, comorbidities, and patient preference will always be important in medical decision-making, and may drive decisions no matter what the molecular profile, in many cases. However, it is not yet time to throw the baby out with the bathwater, based on the evidence presented to date.

Conflict of Interest. The authors declared no conflict of interest.

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