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Editorial

EDITORIAL

Genomically Guided Cancer Treatments: From "Promising" to "Clinically Useful"

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Predictive oncology is a rapidly developing field. The Cancer Genome Atlas and other efforts have shown that amongst a subset of 200 to 500 tumors, there is heterogeneity in the genomic landscape in any tumor, even though certain subgroups can be discerned (1). Some of these molecular abnormalities may be targetable with drugs currently approved or under development. There are now many available opportunities to sequence a patient's tumor in the clinic. While questions remain as to when a tumor should be sequenced, the turnaround time of massively parallel (next generation) sequencing is now two weeks or less, which is within clinical feasibility for deciding on treatment. Reports of "super" or "exceptional" responders and precedent for approval of targeted drugs for more than one malignant condition (eg, imatinib has been approved by the US Food and Drug Administration [FDA] for dermatofibrosarcoma protuberans, myelodysplastic/myeloproliferative diseases, aggressive systemic mastocytosis, hypereosinophilic syndrome/chromic eosinophilic leukemia, relapsed/refractory Philadelphia chromosome positive acute lymphocytic leukemia, as well as for chronic myelogenous leukemia and gastrointestinal stromal tumor) tempt the patient and the clinician to "try" a targeted treatment in a tumor for which it is not approved, but which has the putative target.

Currently, the opportunity is present to use clinical research to help define whether and when sequencing a tumor's DNA will be helpful to the patient. Because many mutations or molecular variants have a low prevalence in any particular tumor type (1% to 10%) based on current databases, clinical trials for each variant in each tumor type will not likely be feasible in any but the most common cancers. Clinical trials investigating the efficacy of targeted treatment in low-prevalence variants will likely need to be different from the standard phase I (dose finding), phase II (early efficacy), and phase III (randomized controlled trial of new vs standard treatment) clinical trials that have been used in the majority of drug approvals by the FDA. To address this issue, flexible trial designs using many different treatments in a single cancer type, depending on molecular characterization or using a single targeted treatment for several tumor types that carry the relevant molecular alteration (2), are underway at many centers. In design of such trials, careful consideration should be given to the choice of primary endpoints and how to measure clinical benefit. A nonrandomized clinical trial, however, will not be able to account for potential prognostic effects of the variant under study. Some molecular abnormalities may be associated with a less rapid progression of tumor; thus, demonstration of prolonged progression-free survival compared with historical controls may be because of differing biology or to the treatment. Objective response rates may be better than expected in a cohort of patients selected by a predictive marker assay, and the duration of that response may indicate clinical benefit. At some point a comparison with how such patients fare with standard treatment may be necessary before declaring the new treatment to be better.

Knowledge about the relationship of mutated genomic variants to clinical behavior of the tumor continues to build. The milieu in which a molecular abnormality exists may influence response to a given agent. For example, upregulation of a resistance pathway may prevent or abrogate a response to a particular targeted agent. This information spurred investigation into resultant activation of certain pathways by the treatment, as well as a search for comutations that could help predict response better (3,4).

Furthermore, in many clinical trials of agents for which evidence supporting FDA approval was found insufficient, one or a few patients have an "exceptional response"—in some cases a complete and durable response. This type of response also occurs in clinical practice. An intense effort to molecularly characterize these tumors, currently ongoing in the National Cancer Institute (NCI) Exceptional Responders Initiative (www.ctsu.org), may lead to hypotheses to explain these responses. Laboratory investigations may be able to enlighten us further on the molecular mechanism of the response. Further work should

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define whether molecular variations can be found in others and whether these others may also respond to similar treatment.

As stated in the article by Meric-Bernstam in this issue of the Journal (5), evidence that a particular mutation, fusion, or copy number alteration actually has an impact in the behavior of a tumor (driver) and/or whether addressing the function of this abnormality with a targeted agent or treatment will affect the progress of the malignancy is needed in order to adequately develop precision oncology. Databases that collect whether a mutation was found in a tumor exist but do not always have information on effect on tumor behavior, nor is there agreement on various standard means of annotation and interpretation of various genomic variants. Harnessing the experience of the many research and clinical laboratories in this area is one of the goals of Clin Gen, a National Institutes of Health–funded resource concerned with discerning which genetic variants influence clinical course or treatment. For genomically guided treatment, there is no consensus on what level of evidence is needed to use a molecular abnormality to choose a treatment. FDA approval for use of a drug or treatment in a patient whose tumor has the desired molecular abnormality, as indicated by an FDA-approved or cleared assay is, of course, a very high level of evidence for a given drug in a given tumor with a given molecular variant. Is it reasonable to use the same drug in a different tumor that has the molecular abnormality, measured by a novel or different assay? Does the abnormality have to be expressed in a substantial proportion of the tumor cells, or is it reasonable to use an abnormality present in only 5% of the "reads" of a next-generation sequencing assay? The NCI–Molecular Analysis for Therapy Choice (NCI-MATCH) trial soon opening in the National Clinical Trials Network will begin to address some of these issues (6). NCI-MATCH is a signal-finding trial, and positive signals will need to be pursued with additional work. Hopefully, results from trials such as NCI-MATCH and other umbrella and basket trials will contribute evidence toward clinical validation and clinical utility of using molecular information to guide cancer treatment. Well-curated databases will aid in this effort.

Note

This work is not necessarily the opinion of the National Cancer Institute, the National Institutes of Health, or the US Department of Health and Human Services.

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