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Editorial

Exceptional Responders Inspire Change: Lessons for Drug Development From the Bedside to the Bench and Back

Nicole G. Chau, Jochen H. Lorch

Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA

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Targeted therapies have changed the landscape of cancer treatment. Unfortunately, the promise of "targeted therapy" still fails too many patients with advanced cancer. Oncologists should ask why and how can we rapidly develop novel strategies. In medicine, exciting and novel occurrences are often first publicized as a case report. This quick yet detailed description of the clinical presentation, diagnosis, treatment, and outcome of an individual patient remains an important part of medical progress. However, although case reports serve as anecdotal clinical evidence that may be shared for educational, scientific, or medical purposes, the amount of information that can be generalized to a wider group of cancer patients is typically limited. Can case reports extend knowledge beyond the single patient experience and offer mechanistic insight or lead to novel therapeutic strategies?

Case Reports of Exceptional Responders Are Inspiring and Can Inspire Change

So-called "Exceptional responders" are a minority of patients with cancer who respond to drugs to an unexpected and often dramatic degree. These drugs, which are typically targeted agents, may or may not be approved by the U.S. Food and Drug Administration (FDA) and may or may not be given in the context of a clinical trial. These cases offer an opportunity to gain insight into the tumor biology and to gain knowledge about an underlying genomic or molecular alteration that is targeted by a particular agent. Several cases have been published to date: for example, an advanced bladder cancer patient who had a durable complete response (measured in years) to the mammalian target of rapamycin (mTOR) inhibitor everolimus and whose tumor harbored a somatic loss-of-function mutation in tuberous sclerosis complex 1 (*TSC1*) [1]. Further studies showed that *TSC1* mutations occur in approximately 8% of patients with bladder cancer, and it is likely that patients with the same or similar mutations would benefit from mTOR inhibition as well. Notably, this patient was treated in a phase II trial that failed to reach its progression-free survival endpoint. In the past, further development of the drug in this disease would have ceased because the efficacy signal would have been too weak to be picked up in classical statistical trial analysis. This example highlights the drawback of summarizing response data to conclude absence of activity and the worthiness of in-depth interrogation of exceptional responders. Another example is a patient with metastatic urothelial carcinoma who had a 14-month complete response to everolimus and pazopanib on a phase I trial and whose tumor was found to have two concurrent activating mutations in mTOR not previously described in human tumors [2].

Exceptional responders can also shed insight into mechanisms of resistance, because tumors driven by a dominant oncogene will invariably develop resistance to targeted drugs. For example, another exceptional response to everolimus in a patient with metastatic anaplastic thyroid cancer, a cancer associated with median survival of 5 months, was published recently by our group [3]. The patient had a near-complete response lasting 18 months and whole-exome sequencing revealed a novel, somatic inactivating *TSC2* mutation, explaining the tumor's exquisite sensitivity to mTOR inhibition [3]. Furthermore, upon progression, biopsy of the resistant tumor revealed a novel, secondary somatic mutation in *mTOR* (F2108L) conferring resistance to allosteric mTOR inhibition. However, because this mutation occurs in the FK-506 binding protein-rapamycin-binding domain rather than the active site, in vitro studies of the mutant protein demonstrated retained sensitivity to direct kinase inhibition with ATP-competitive TOR kinase inhibitors. Therefore, comprehensive serial analysis of exceptional responders with sequential biopsies can identify secondary resistance mechanisms and therapeutic strategies to overcome them. For instance, based on these data, a phase II study of the mTOR kinase inhibitor MLN0128 is set to open soon for patients with anaplastic thyroid cancer, including those who have previously failed everolimus.

From Targets to Therapeutic Trials

The promising clinical activity of these unique responders, and the availability of affordable and rapid gene sequencing has led to ongoing efforts to perform routine genomic profiling

Correspondence: Jochen H. Lorch, M.D., Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Avenue, D2136, Boston, Massachusetts 02115, USA. Telephone: 617-632-3090; E-Mail: Jochen_Lorch@dfci.harvard.edu Received December 12, 2014; accepted for publication April 15, 2015; published Online First on June 3, 2015. 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2014-0476

of cancer patients at major academic institutions. This information can be used for the increasing number of "basket" trials, which select for patients with specific genetic markers across multiple cancer types to test targeted therapies. As an example, academic institutions such as Memorial Sloan Kettering Cancer Center, the Dana-Farber Cancer Institute, Massachusetts General Hospital, Vanderbilt University Medical Center, and MD Anderson Cancer Center, among others, offer patients comprehensive tumor profiling with an in-house targeted next-generation sequencing platform to facilitate entry onto biomarker driven clinical trials. Commercial tumor sequencing is also available and may be become eligible for coverage through health insurance in the near future.

Practically operationalizing this technology for clinical benefit requires prompt turnaround of results in patients who are fit, are willing, and have access to clinical trials with matched therapies. Unlike with testing for a limited number of defined, actionable hot spots such as v-raf murine sarcoma viral oncogene homolog B (*BRAF*) or epidermal growth factor receptor (*EGFR*) mutations, much work is still needed to assist clinicians and patients in the interpretation of massive amounts of sequencing data and help to distinguish between clinically actionable, so-called driver events that enhance cancer cell fitness from the much larger set of passenger alterations that are present in tumor DNA. The interpretation of sequencing reports can be especially challenging when multiple seemingly significant genomic alterations are identified or new mutations of unknown biochemical or molecular significance are found. Sequencing data are typically analyzed in a three-step process: sequence alignment, variant identification, and molecular annotation of variants [4]. In the first step, data are aligned with the reference genome, a time-consuming process that requires extensive computational capabilities. Variant identification is achieved through a number of analytical tools, and in the case of limited gene panels, this step is frequently omitted, and one can proceed directly to the annotation of variants. However, although relatively fast and providing useful information in many cases, it may be difficult to distinguish between rare germline events versus bona fide somatic tumor mutations, which may still potentially represent useful clinical targets. Therefore, whole exome and genome sequencing always requires comparison of the tumor genome with the germline from the same individual to identify true somatic variants. In the final step, results are annotated to translate raw genomic information into clinically useful reports. Because of the large amount of data that is condensed into a easily understandable, concise, and clinically useful document, potentially important information can be lost at any one of these steps and can limit or provide misleading information for clinical decision making [5]. Challenges include the possibility of finding multiple potential drivers that could be passenger mutations without therapeutic potential. Genetic tumor heterogeneity can obscure the picture because the mutational landscape usually varies between different tumor samples, as well as tumor samples from different metastatic sites [6, 7]. When novel variants are identified, it may be impossible to determine their biologic significance without further extensive testing in the laboratory.

Additional testing such as full genomic or transcriptome analysis may also be necessary to detect rearrangements such as anaplastic lymphoma kinase (*ALK*) fusions because exome sequencing typically does not capture the relevant intronic sequences. Much work is necessary, and providing the necessary tools to analyze, annotate, and clinically interpret sequencing results will remain an area of active research in the years to come.

As these new tools become increasingly available, the industry recognizes that drug development can be accelerated when new targeted agents are tested in patient populations with specific biomarkers and where high response rates may be anticipated. Under these circumstances, phase I testing may be sufficient to obtain approval from the Food and Drug Administration (e.g., ceritinib in *ALK* rearranged non-small cell lung cancer) [8]. Many industry-sponsored trials offer tumor prescreening for specific biomarkers to determine eligibility and frequently require mandatory fresh serial tumor biopsies. Larger industry-sponsored initiatives, such as the Novartis "Signature" Program (https://www.signaturetrial.com/en), were recently launched to provide the specific targeted basket trials for matching genetic variants at participating institutions. These academic and industry-sponsored initiatives are in parallel to recently launched nationwide collaborative efforts, such as the NCI-MATCH (Molecular Analysis for Therapy Choice) [9], a large-scale umbrella trial initiative that uses next-generation sequencing assays of patients' tumors to assign patients to rationally targeted therapies and offers patients tumor rebiopsy and sequencing upon progression to evaluate resistance mechanisms. According to the NCI, approximately 1%–10% of patients are exceptional responders, broadly defined as those who achieve complete or partial response lasting at least 6 months in response to a drug that did not go on to FDA approval in that indication because of insufficient activity in an unselected population.

Future Directions

Insight gained from an exceptional responder has the power to identify new biomarkers of sensitivity that can unlock subsets of patients across anatomic disease sites who may also derive benefit and facilitate the development of novel therapeutic strategies that may overcome resistance. In our opinion, the use of large-scale genomic profiling is a promising first step. In the future, comprehensive profiling including immune markers, epigenomics, and proteomics will also develop greater clinical application as technologies evolve and costs decrease. Learning from exceptional responders requires tremendous collaboration, funding, and translational infrastructure to perform biopsies (including serial biopsies) and thorough tumor analysis. It also demands greater dedication in clinical trials to perform in-depth tumor interrogation and correlative studies to ask why and how rather than focus solely on collective response rates. We believe that studying extraordinary clinical responders can benefit a

larger community when exceptional research efforts are applied.

Author Contributions

Conception/Design: Nicole G. Chau, Jochen H. Lorch
Provision of study material or patients: Nicole G. Chau, Jochen H. Lorch
Collection and/or assembly of data: Nicole G. Chau, Jochen H. Lorch
Data analysis and interpretation: Nicole G. Chau, Jochen H. Lorch
Manuscript writing: Nicole G. Chau, Jochen H. Lorch
Final approval of manuscript: Nicole G. Chau, Jochen H. Lorch

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