EDITORIAL

Have Mutation, Will Travel

Utilizing Online Patient Communities and New Trial Strategies to Optimize Clinical Research in the Era of Molecularly Diverse Oncology

Howard (Jack) West, MD,* and D. Ross Camidge, MD, PhD†

Our conceptualization of oncology is undergoing a revolutionary transition based on advances in the molecular categorization of cancer. This recognition of the importance of molecular diversity has led to clear advances not just in the understanding of, but in the targeted treatment for, specific and increasingly narrow subtypes of many cancers. Using lung cancer as an example, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors or crizotinib have been clearly demonstrated to produce response rates in the 60 to 75% range and prolonged progression-free survival in the range of 9 to 13 months when given to patients with an activating EGFR mutation1–4 or anaplastic lymphoma kinase (ALK) translocation,5 respectively. Although these results represent treatment breakthroughs for subgroups of patients, the implications for clinical research focusing on cancer patient subpopulations are only just becoming apparent.

The frequency of EGFR mutations varies geographically but is present in only approximately 10 to 15% of the Caucasian lung cancer population. ALK gene rearrangements are present in only approximately 4% of cases from series containing predominantly adenocarcinoma of the lung.6,7 Recently, the US-based Lung Cancer Mutation Consortium tested for 10 different potentially “druggable” molecular abnormalities in 1000 patients with advanced lung adenocarcinoma. Among the data available from the first 516 fully analyzed cases, 54% had an identified abnormality, with 97% of these being mutually exclusive.8 After KRAS mutations (22%), EGFR mutations, and ALK gene rearrangements were accounted for, the other seven abnormalities together represented less than 8% of the total non-small cell lung cancer population.

As most of the agents with the potential to act on a specific molecularly defined subset are only available within clinical trials, how do we conduct a trial when the requisite patients are geographically diluted, and even a large center may only see one or two cases of a particular molecular subtype in a given year? Conversely, if you are a patient and learn that you fall within a specific molecularly defined subgroup, how do you get access to the best information and treatment on your disease when even the most common cancers are now fragmenting into rare subdiseases? The greater magnitude of potential benefit with more carefully selected matching of treatment to patient subpopulations now raises the value for patients to pursue them across significant distances. The success of such a model is predicated on patients and caregivers having access to high-quality, timely information about emerging therapies, without misrepresenting the potential clinical benefits for trial participants. Essentially, this means good communication between knowledgeable physicians and an engaged patient community. These opportunities have become increasingly available through channels such as American Society of Clinical Oncology’s patient website (www.cancer.net) and a growing collection of other high-quality educational resources.

*Swedish Cancer Institute, Seattle, Washington; and University of Colorado, Anschutz Medical Campus, Aurora, Colorado.

Disclosure: D. Ross Camidge, MD, PhD, has received honoraria from Pfizer, Inc., for ad hoc advisory boards.

Address for correspondence: Howard (Jack) West, MD, Swedish Cancer Institute, 1221 Madison Street, Suite 1020, Seattle, WA 98104. E-mail: howard.west@swedish.org

Copyright © 2012 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/12/0703-0482

Journal of Thoracic Oncology • Volume 7, Number 3, March 2012

482

Copyright © 2012 by the International Association for the Study of Lung Cancer.
One of us (H.J.W.) leads a free social media-based community for patients along with their caregivers called the Global Resource for Advancing Cancer Education (GRACE) (www.cancergrace.org), which provides an ongoing stream of medically curated content as well as an interactive question and answer forum moderated by a rotating panel of expert cancer clinicians. Although covering several different cancers, to date it has mostly focused on lung cancer. In February 2010, GRACE hosted a podcast by one of us (D.R.C.) on the emerging ALK story in non-small cell lung cancer, explaining the details and location of the ongoing crizotinib trials and the requirements for proven ALK positivity before study entry. The podcast has since been streamed or downloaded more than 1300 times, primarily by patients and caregivers. Until the last crizotinib lung cancer trials closed to accrual in 2011, patients had traveled to the University of Colorado’s lung cancer program from 15 different US states and one non-US country (South Africa) to pursue the opportunity to participate in clinical trials with this agent. Of note, the University of Colorado has traditionally conducted very little direct-to-patient advertising locally and none either nationally or internationally. Therefore, GRACE and other online lung cancer patient support communities, along with news media coverage, are likely to represent the dominant sources informing patients living outside the state of the study’s presence at the University of Colorado.

Molecular drivers of cancer and their potential to derive benefit from specific therapies are likely to cross traditional tumor type-specific boundaries—e.g., ALK gene rearrangements and responses to crizotinib have also been reported in patients with inflammatory myofibroblastic tumors, a rare sarcoma. Reorganizing information resources along molecular lines in response to new data may prove to be far easier within online communities than it will be within the established tumor type-specific practices of community and academic oncologists.

How can we address the logistical challenges of conducting clinical trials among geographically dispersed and molecularly diverse populations, beyond the initial optimization of information and mutual support for potential participants in online communities? Dramatically streamlining the opening of clinical trials could be one solution—essentially adopting an “off-the-peg” trials approach so that having found a patient with a molecular abnormality, access to the drug in a trial can be brought quickly and efficiently to the patient at their nearest treating facility. Although this sounds simple, the challenges associated with such an approach would be considerable. Clinical trials are very carefully regulated, and clinical trial sites and investigators are carefully monitored. Although undoubtedly inefficiencies in the process exist and could be improved upon, bringing the trial to the patient in a timeframe that is unlikely to compromise their clinical care, but which preserves Good Clinical Practice and remains in accordance with the Declaration of Helsinki, would be hard to achieve. Alternatively, for patients who already know or suspect their molecular abnormality but would need to travel a significant distance for experimental therapies, several developments would significantly facilitate clinical research in this setting, beyond simply including some travel and overnight accommodation reimbursement within study budgets. At present, patients usually travel to involved sites to offer their consent and then return to be screened for the trial, necessitating several different trips before treatment starts. Phone consultation followed by the exchange of consent forms via fax or e-mail before a first visit is eminently feasible but currently not reimbursed by most...
insurers or in most study budgets. Moreover, most scans, routine laboratory tests, and electrocardiograms are conducted on site during a clinical trial, but using local facilities with their associated normal ranges for laboratory values should also be feasible for some “visits,” and imaging distantly and relaying to the treating center could also be possible if the software for viewing images can be better standardized across centers. Instead of traveling on days without treatment, toxicity checks could be conducted over the phone or via Health Insurance Portability and Accountability Act-compliant, encrypted video links, and local practitioners could conduct standardized physical examinations if these and the oversight and coordination time involved were reimbursable.

If the molecular abnormality is not yet proven within an individual patient’s tumor, additional challenges will arise. Pharmaceutical companies pursuing molecularly specific licenses for their drug will usually file in conjunction with data to support a specific companion diagnostic. To ensure standardization, such testing may need to be conducted within a central testing facility. Although in the initial crizotinib trials many patients were required to travel to study sites simply to sign a prescreening consent form that allowed their tumor to then be sent for central testing, there is no reason to follow this precedent. Again, phone consent for prescreening and addressing shipping costs and coordination costs to facilitate this process without the patient having to travel before receiving a positive screening result are all relatively easily achievable changes to facilitate clinical research across disparate populations. When community testing for a marker is available, additional opportunities exist. In this scenario, sponsors could permit study entry based on locally developed tests and then follow this with retrospective central confirmation, recognizing but accepting that the number of evaluable centrally positive cases will inevitably be smaller than the total number enrolled on the study.

Even with such improvements, a sponsor is still charged with the decision of where to open such molecularly specific trials. As described above, “off-the-peg” models designed to bring the trial to the patient in real-time are likely to be problematic. Instead, sites currently, and for the foreseeable future, are chosen well in advance of the first eligible patient being identified. Realistically, it may be most economically feasible to pursue a new model that involves opening molecularly specific trials at a few geographically dispersed centers and requiring motivated patients to travel to an accessible center, rather than the alternative of opening the same trial in large numbers of low accruing sites. The striking similarity of Figure 1 to an airline’s network of connections utilizing key “hubs” located across the country raises the question of whether a similar model utilizing “trial hubs” should actively be pursued for clinical research involving rare cancers/molecular subgroups.

The last decade has ushered in a sea change in the practice of oncology, largely as a result of new molecularly defined subgroups being identified within what were previously perceived as monolithic broad cancer populations. This transition has led to remarkable benefits when narrower subsets of patients have been the optimal beneficiaries of a novel, molecularly guided therapy, but it has also introduced practical challenges in which the low geographic density of these newly defined subgroups have made it increasingly difficult to follow traditional models for clinical research. The oncology and pharmaceutical communities now have the option of adapting to this new era in a number of different ways. Online patient communities can now be leveraged to partner with clinical researchers in getting patients appropriately informed and motivated. Clinical trial costs, conduct, and site locations can all be modified to overcome many of the geographic limitations. The proposed changes may be new, but they are not hard to achieve. In this we are fortunate, for only by embracing the practical reality of cancer’s increasingly revealed diversity will we be able to capitalize on and accelerate the pace of molecularly guided clinical research in the future.

REFERENCES