CONFERENCE SCENE

Colorectal Cancer

Fighting a smarter war against cancer

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News & Views

News

Conference Scene

Molecular Profiling in Cancer: Research or Practice, Georgetown University Hotel and Conference Center, Washington, DC, USA, 6–7 December 2013

On the 6th and 7th of December 2013, the Ruesch Center for the Cure of Gastrointestinal Cancers (DC, USA) hosted its fourth annual symposium entitled Molecular Profiling in Cancer: Research or Practice. This topic was selected for the 2013 symposium because of the explosion of molecular profiling assays that are available to us as practicing oncologists, which are believed, by most, to be a significant advancement in cancer care innovation. The Ruesch Center has been hosting topical symposia for the last 4 years. We have focused on: biomarker use in cancer medicine (2010); defining value in cancer care (2011); how to engage the 'other 97%' of patients in clinical trial enrollment, when currently we capture only 3% of patients on average (2012); and, of course, molecular profiling in cancer care (2013).

Molecular profiling: a summary

Molecular profiling, as you are most likely aware, is a broad term encompassing genetic or protein testing performed on patients' tumors or other tissues, with the aim of characterizing their individual gene or protein profiles. Following such testing, the ideal scenario is that drug selection or drug dosing can be optimized for individually improved clinical outcomes (otherwise known as personalized medicine).

Our current world of cancer medicine involves the pure empiricism of trial and error, which is guided by only a handful of molecular tests. Certainly in gastrointestinal (GI) cancers, the only significant molecular testing that occurs is *KRAS* testing for colorectal cancer [1] (soon to be 'general' *RAS* testing [2]) and HER2/neu testing for gastric cancer [3]. Other GI cancers are treated essentially empirically using standard-of-care practice guidelines. However, fundamentally, we recognize that all patients we are treating, and all cancers we are fighting, are indeed different and yet we treat them using the same practice guidelines. The profiling assays available to us are innumerable and, although costly, they are not out of reach; many are in fact covered by patients' health insurance. Could we actually take the emerging technology of molecular profiling and somehow change our standards of care, utilizing profiling test results to obtain that ideal scenario of individual drug selection and improved patient outcomes?

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Thus, the purpose of our 2013 symposium was to bring together a multidisciplinary group of cancer care stakeholders and experts to debate the merits of molecular profiling, the different assays that are available and how molecular profiling impacts patients in their current day-to-day care. In essence, is this technology still research or has it already moved into the realm of current oncologic practice?

Molecular profiling is indeed an incredible technology and something we strongly believe we should pursue. However, does molecular testing truly reflect the tumor we are treating? We recognize significant tumor heterogeneity and the evolution of tumor profiles over time. A new primary tumor clearly has different gene expression compared with that observed once it has metastasized and become refractory to treatment. So the logic of taking a distant tumor sample and applying that molecular profile to a current treatment paradigm is potentially misguided.

The actual choice of molecular entity to measure is another point of contention. There are those that believe the answer is in the protein, while others believe it is in the DNA or RNA profile [4,5]. Newer technologies, such as miRNA, metabolomics, and even chemosensitivity assays, are all available to us. Even at the protein level, further analyses are available that evaluate phosphorylated proteins (phosphoproteins) [6]. These analyses determine which pathways are actually activated within a tumor. The question remains as to whether we actually need tumor tissue for many of these tests or whether a simple blood sample could be a viable option to measure the unique molecular characteristics of a patient and their tumor, and thus enable personalized treatment decisions.

In early December 2013, the US FDA actually cleared next-generation (DNA) sequencing for routine medical care. FDA approval of gene sequencing assays is a landmark moment for the world of molecular profiling.

Our current state is that we can certainly order the tests and get a report back, often an extensive multipage report, outlining not only the gene profile of a patient's tumor but also multiple references to possible clinical trials for that patient. I cannot help being influenced by these reports, but it is unclear to me whether they are a distraction or, in fact, the correct way forward for our patients. Some circumstances are quite easy to interpret. For example, if a molecular profile suggests that treatment A is better than treatment B and both A and B are approved for the same patient situation, of course I would give A. However, if A is unapproved for that indication or is indeed an investigational agent and B is the standard-of-care approach, I am not sure I am prepared to forego treatment B in that patient based purely on the molecular-profiling assay. Recently, I have seen a number of automatically generated post-tumor molecular-profiling reports that indicate that the best course of action is to administer the very treatment that the patient last progressed on. This is a concern, and if molecular testing and automated report generation is to become the standard-of-care, we certainly need an improved process. We also have to recognize that not all mutations behave the same in every disease. The most striking example involves the occurrence of mutations in the *BRAF* gene: detection of these mutations is very useful in the treatment of melanoma, but in metastatic colon cancer, the use of mutant *BRAF* as a single-drug target has failed to show any benefit.

We like to anticipate that in the not too distant future, molecular profiling will predict the right treatment for the right patient, and patient outcomes will improve. We also foresee changes in our regulatory systems that will support drug approvals for novel gene targets instead of for diseases and lines of therapy. This being the case, we should be able to replace safety and efficacy evaluations with a value metric for drug approval. Drug safety and efficacy approval goals result in large randomized clinical trials that cost hundreds of millions of dollars to perform, with the end point of improving overall survival measured in weeks instead of months, and certainly nowhere near a cure. The theory is that targeted therapy that leads to less toxicity, is more likely to be efficacious in carefully selected patients (via molecular profiling), and is more likely to cost much less money before being granted approval by the FDA. The rest of the world applies the additional standard of 'value' to new drug approvals. It is of utmost importance that US payers recognize the new indications discussed in this report, and that hopefully, over time, costs will fall and we will have significantly less trial and error and more cancer treatment success stories.

How far are we from this new world? Is it just around the corner or are we still at the earlier stages of metamorphosis, in our cocoons,

transforming a little at a time until we blossom into the world of molecular profiling?

Ruesch Symposium: a summary

The Ruesch Symposium engaged an incredible faculty, and we divided our event into two parts. The first was a series of didactic lectures for the multidisciplinary participants, including presentations from innovative leaders in molecular profiling, Centers for Medicare and Medicaid Services, and the FDA. This set the stage so that everyone in the room understood the concept, the pros and cons, the barriers, the laws and the latest innovations in the field of molecular profiling.

We then shifted into a multidisciplinary tumor board-based series of presentations. Three patient cases were presented by their treating physicians and the patients themselves to a panel of stakeholders, which included leaders from the pharmaceutical industry, GI cancer experts and molecular profilers. All patient cases involved molecular profile-directed treatment, which was discussed by the panel with the physician and patient.

Our physician education in US medicine rarely includes actual patients as participants; they are almost always on the 'other side of the door'. One of our fundamental beliefs within the Ruesch Center is that patients must be involved in decision-making at the highest level. The impact of having the actual patient with metastatic disease, whose tumor was profiled, standing in front of this incredibly bright group of scientists and researchers was truly remarkable. The tone of the entire session shifted away from a purely objective scientific outlook to one with a human face and human consequences. How were we going to help this person? This was no longer abstract or theoretical. One of the most striking moments was when a patient asked the panel whether, if they currently had cancer, they would want their tumor to undergo molecular profiling, and across the board every panel member said 'yes'. They would want this test, not because they would know exactly what to do with it but because it would influence their decision-making going forward.

We learned a great deal during the course of this meeting. We learned about the cutting edge science and technology behind molecular profiling and its impact on us as human beings today.

As a group, our conclusive recommendation is to move forward with this type of technology. While it remains wedged between research and clinical practice, we believe that its incorporation into clinical research and, in fact, into everyday practice (along with good documentation of outcomes) is the only way that we will emerge from our cocoon and, indeed, fly into the next generation of cancer care incorporating molecular profiling.

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References

1 Allegra CJ, Jessup JM, Somerfield MR *et al.* American Society of Clinical Oncology provisional clinical opinion: testing for *KRAS* gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J. Clin. Oncol.* 27(12), 2091–2096 (2009).

2 Peeters M, Oliner KS, Price TJ *et al.* Analysis of *KRAS*/*NRAS* mutations in Phase 3 study 20050181 of panitumumab (pmab) plus FOLFIRI versus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC). *ASCO Meeting Abstracts* 32(Suppl. 3), Abstract LBA387 (2014).

3 Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann. Oncol.* 19(9), 1523–1529 (2008).

4 Caris Life Sciences. www.carislifesciences.com

5 Foundation Medicine. www.foundationmedicine.com

6 Theranostics Health. www.theranosticshealth.com