SPRING 2017, VOL. 6, NO. 2

Pathways in Cancer

Clinical insight and analysis in advanced cancer care

The Case for Precision Medicine

Shahzad Siddique MD

Precision medicine is also referred to as personalized medicine and individualized medicine. In oncology, one application is the use of gene expression profiling to inform specific therapy. These targeted therapies are often less toxic and more effective. There are multiple targeted therapies that are currently commonly used in cancer care. The cost of genomic testing continues to come down, making more extensive testing more feasible. Many hospital systems and academic centers are building programs to make testing more accessible for their providers.

One of the earliest forms of targeted therapies in oncology is the use of tyrosine kinase inhibitors in chronic myelogenous leukemia (CML). CML is a myeloproliferative neoplasm associated with a chromosome 9 and 22 translocation resulting in the BCR-ABL fusion gene. This results in the formation of the BCR-ABL protein which is a constitutively active tyrosine kinase. This genetic abnormality can be targeted by a class of drugs known as tyrosine kinase inhibitors (e.g., imatinib, dasatinib, and nilotinib). These drugs have revolutionized the care of CML. CML has changed from a fatal disease to a chronic one that can now be managed with oral therapy. Lung cancer is now also defined by molecular subtypes. Oral medications that target the EGFR and ALK mutations are now used in first line therapy. These medications are often less toxic and associated with an increase in overall survival. Breast cancer is now thought of as a heterogeneous disease with distinct subtypes with variable behavior. There are three subtypes based on gene expression profiling including luminal, human epidermal growth factor 2-enriched (HER-2), and basal. HER-2 is an oncogene expressed in approximately 20% of primary invasive breast cancers. A number of drugs that target HER-2 including trastuzumab, pertuzumab, lapatinib, and ado-trastuzumab emtansine are used in both the adjuvant and metastatic setting.

There are multiple different approaches to genetic testing in cancer. Next-generation sequencing technologies allow for sequencing of the coding region of entire human exome (all regions that encode for a protein) or genome with costs rapidly approaching the $1,000 price point. This extent of analysis is generally done for research purposes. A more common application is the interrogation of the genome for a limited panel of known cancer causing genes (ranging from 10 – 300+). This form of targeted gene panel testing is increasingly being offered by commercial labs and used for patients with advanced stage cancer.

The cost of genomic testing continues to come down, making more extensive testing more feasible. Many hospital systems and academic centers are building programs to make testing more accessible for their providers.

Due to advances in technology, oncologists now have a number of additional tools available to deploy personalized molecular therapies for their patients. There are a number of unanswered questions about the best approach towards using these tests. We need to determine the most clinically effective way to use these tests, and the most cost effective approach. There are challenges with obtaining reimbursement from insurers. We need to determine if this approach towards cancer results in improved survival in all cases. Physicians also need guidance in interpretation of these tests and assistance in procuring medications. Therefore, the best approach towards the use of precision oncology is a system-wide coordinated program.

The Precision Medicine Alliance (PMA) is a joint venture between Dignity Health and Catholic Health Initiative (CHI). The purpose of the company is to structure and deploy precision medicine-based products and services across multiple geographic markets. The PMA will develop direct relationships with lab and software vendors to automate the process of ordering and reporting test results. This will allow the health systems to collect data and use this information to develop

continued on page 3

Dignity Health
Cancer Institute of Greater Sacramento

Genomic Diagnoses and Pharmacology

Grigorios Chrysofakis, MD

Multiple significant changes have taken place in the U.S. health care system over the past decades. Medicine has been undergoing a deep transformation. This shift is moving medicine from an endeavor in which care for individual patients is driven by studies designed to measure population outcomes to one in which care is selected based on a deep understanding of health and disease attributes unique to each individual.

Accelerated by the completion of the Human Genome Project in 2004, this transformation has been variably called genomic medicine, genomic health care, personalized medicine, precision medicine, and precision health.

The evolution of science and technology has shed light on some aspects of molecular genetic or biochemical testing which guides diagnostic evaluation of tumors, selection of treatments, and provision of prognosis.

The exact definition of precision medicine is a moving target. The National Institutes of Health (NIH) defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in environment, lifestyle and genes for each person." The National Academies of Science, Engineering, and Medicine recently renamed the "Roundtable on Translating Genomic-Based Research for Health" to "Roundtable on Genomics and Precision Health."

For most clinicians, the benefits of the global push into precision health have been slowly accumulating. This has been a cornerstone in the modern approach of hematological and oncological diseases. The evolution of science and technology has shed light on some aspects of molecular genetic or biochemical testing which guides diagnostic evaluation of tumors, selection of treatments, and provision of prognosis.

The role of precision medicine in diagnosis of hematological and oncological disorders is very clear. Often disease is caused by mutation in a single gene. Some of these disorders present as germline (inherited) mutations whereas others are acquired. Examples of the former are disorders such as sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and factor V Leiden, which are common, whereas others (such as chronic granulomatous disease) are rare. All are caused by mutations in a gene that result in the formation of a defective protein or an insufficient amount of a normal protein. Examples of the latter are a number of acquired hematologic and oncological diseases, including lymphomas, leukemias, and other clonal hematologic diseases. All are consequences of acquired damage to the genetic apparatus.

Personalized medicine also plays a pivotal role in identifying genetic alterations, which have prognostic and management implications for many inherited malignancies. One of the most well known is the mutation in the Breast Cancer Susceptibility Genes (BRCA) 1 and 2. These risks are not isolated to women, but also impact men who inherit this mutation.

In women, the most common cancers related to these mutations are primary and secondary breast cancer, ovarian cancer/primary peritoneal carcinoma, uterine papillary serous carcinoma, and pancreatic and colorectal carcinomas. In men, the most common are male breast cancer and prostate cancer. Knowledge of presence of these mutations can lead to additional risk-reducing strategies. For example, a woman with breast cancer, or a family member of a patient with breast cancer, may undergo bilateral mastectomy and bilateral salpingo-oophorectomy, more intensive screening (e.g., breast MRI) or other options.

Another paradigm of mutations which has prognostic and predictive value is the germline mutations in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene. This is described as Lynch syndrome and is the most common cause of inherited colorectal cancer. It is also characterized by a significantly increased risk for endometrial cancer as well as a risk of several other malignancies. Colon cancer in Lynch syndrome is predominantly right-sided. Although the cancer appears to evolve from adenomas, the adenomas tend to be larger, flatter, more often proximal, and more commonly with high-grade dysplasia and/or villous histology as compared with sporadic adenomas. The adenoma-carcinoma sequence also progresses much more rapidly in Lynch syndrome as compared with sporadic colon cancer. These tumors are usually less aggressive (usually stage I or II) and are usually associated with better prognosis (prognostic value). In addition, it seems that adjuvant fluoropyrimidine-based chemotherapy is less beneficial or even harmful for these colon cancers (predictive value).

Lastly, a discussion about precision medicine would be incomplete without mentioning the field of pharmogenomics. This refers to the investigation of genes that can predict responsiveness to a specific drug so as to increase the number of responders and decrease the number of subjects affected by adverse drug reactions.

Personalized medicine also plays a pivotal role in identifying genetic alterations, which have prognostic and management implications for many inherited malignancies. One of the most well known is the mutation in the Breast Cancer Susceptibility Genes.

Pharmacogenomics can be broken down into two basic categories: pharmacogenomics of tumor response (more on that by Dr. Siddique) and pharmacogenomics of chemotherapy drug toxicity.

Common examples of pharmacogenomics of chemotherapy drug toxicity are the following:

DPD (dihydropyrimidine dehydrogenase) is the metabolic enzyme of 5-flurouracil and its oral prodrug capecitabine. These two drugs are the cornerstone of colorectal and other cancers' treatment. Checking for mutations in this enzyme can avoid the risk of severe and potentially fatal reactions.

Cytochrome P450 2D6 is the key enzyme that converts tamoxifen to endoxifen. Tamoxifen is a selective estrogen receptor modulator, which is used in hormone receptor-positive breast cancer in a localized and metastatic setting. A direct relationship between endoxifen and its antiestrogenic effects have been documented. Depending on the genotype, patients can be classified as high responders or low responders.

Despite known polymorphisms in both drug metabolizing and transporting proteins that influence drug exposure and pharmacokinetics in patients receiving anticancer agents, and the availability of testing for many of these polymorphisms, genotyping has not become widespread or widely accepted for any of these drug classes.

A Word from Dignity Health Cancer Institute of Greater Sacramento

In our ongoing efforts to diagnose and treat cancer, there are a number of timely developments I'm eager to share with readers.

Oncoverse operates a digital platform that enables health care professionals to collaborate on cancer care decisions and monitor the progress of patient therapies. It is undergoing testing in the Sacramento region to improve capabilities as a virtual tumor board with new features including videoconferencing to allow DHCI physicians to discuss cases conventionally, remotely, and in real time. More to come on this exciting development.

Skin cancer is the most common form of cancer. Knowing prevention tips and recognizing the signs can be empowering and even save lives. **Dignity Health Cancer Institute is hosting a free skin cancer event** Thursday, June 22 at the Davis Chamber of Commerce where attendees can receive a free mole screening; hear from Debra A. Horney, MD on the "Slip-Slap-Slop" campaign, screening, and the importance of early detection; and meet Sonia Reichert, MD—a member of our cancer care team. For more information or to RSVP, contact Community Outreach Coordinator Angela Gianulias at 916.962.8893.

Costanzo Di Perna, MD
Medical Director, Dignity Health Cancer Institute

Continued from page 1, The Case for Precision Medicine

clinical trial portfolios. Further opportunities exist to serve patients and providers through specialty pharmacy services, molecular tumor boards, and educational programs.

Newly emerging molecular technologies have brought a new era of therapy for oncologists. As we learn more about the biology of various cancers, we are realizing many cancers have a distinct molecular signature. The fluid nature of developing technologies has resulted in many challenges for front line providers including access to appropriate tests, reimbursement, and procurement of medication. The PMA is one system-based approach to assist clinicians and patients in getting personalized therapy in their community. Our goals are to simply provide cancer patients the ability to get state-of-the-art molecular testing, the most effective therapy, and the best quality of life closer to home.

Dignity Health
Cancer Institute of Greater Sacramento

6403 Coyle Avenue, Suite 200
Carmichael, CA 95608

CANCER CONFERENCES

For each of our Cancer Conferences, physicians are eligible for 1 CME credit.

To present a case at an upcoming Cancer Conference, please email, fax, or call contacts noted below. To present a case, please provide:

- **Patient's name**
- **Date of birth and/or medical record number**
- **Disease site**
- **Diagnosis**
- **Where path and imaging can be found**

Hospital Cancer Conferences

Mercy General Hospital
Wednesdays at 12:30 p.m.
Location: EW Auditorium
Contact: Jennifer Gutierrez
jennifer.gutierrez2@dignityhealth.org
916.736.8074 (phone)
916.736.8078 (fax)

Mercy San Juan Medical Center
Thursdays at 12:30 p.m.
Location: Conference Room 2
Contact: Wendy Ringer
wendy.ringer@dignityhealth.org
916.962.8799 (phone)
916.536.3044 (fax)

Methodist Hospital of Sacramento
3rd Friday of each month at Noon
Location: Bistro Conference Room
Contact: Lisa Dix
ldix@uscmc.com
916.683.9616 (phone)
916.688.1320 (fax)

Woodland Healthcare
Tuesdays at 12:15 p.m.
Location: DCR 5
Contact: Lisa Manas
lisa.manas@dignityhealth.org
530.662.3961 (phone)

TUMOR-SPECIFIC CANCER CONFERENCES

Breast Cancer Conference
1st and 3rd Tuesday of each month at 12:30 p.m.
Location: Mercy Cancer Center
3301 C Street, Suite 550
Large Conference Room
Contact: Jennifer Gutierrez
jennifer.gutierrez2@dignityhealth.org
916.736.8074 (phone)
916.736.8078 (fax)

GU Cancer Conference
4th Tuesday of each month at 7:30 a.m.
Location: Mercy San Juan, CC3
Contact: Mark Cruz
mark.cruz@dignityhealth.org
916.537.5069 (phone)
916.536.3044 (fax)

Cases may be brought directly to the conference. Pathology and imaging will not be routinely ordered unless there is a question regarding the results.

Neuro-Oncology Cancer Conference
1st and 3rd Thursday of each month at 7:30 a.m.
Location: Mercy Cancer Center
3301 C Street, Suite 550
Large Conference Room
Contact: Mark Cruz
mark.cruz@dignityhealth.org
916.537.5069 (phone)
916.536.3044 (fax)

Thoracic Cancer Conference
Wednesdays at 4 p.m.
Location: Mercy San Juan, CC4
Contact: Kay Habal-Nagtalon
kay.habal-nagtalon@dignityhealth.org
916.962.8798 (phone)
916.536.3044 (fax)

Cases may also be brought directly to this conference.