Pharmacogenomics is Changing Oncology
5 Things You Need to Know Now

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What Does Pharmacogenomics Mean to Oncology?

Pharmacogenetic testing provides information about a patient’s likelihood to have a therapeutic response and/or an adverse reaction to a medication, enabling the potential for a tailored and personalized approach to medication therapy. Genetics has been estimated to account for anywhere between 20% and 95% of the variation in individual responses to medications. When it comes to chemotherapy, the potential for complications is very high and must be carefully weighed against the benefit and overall outcome for each patient. Thus, a treatment regimen should be tailored to the tumor’s genotype in order to optimize the patient’s response. To minimize potential patient side effects, a patient’s genetic profile can help identify how they will metabolize and respond to the treatment.

1 Evolving Treatments Mean Evolving Trial Designs

The traditional treatment path for cancer has been tumor biopsy, histologic diagnosis, and a standard chemotherapy regimen. However, we’ve learned that one size does not fit all when it comes to treating cancers. The traditional approach does not account for the variability between tumors or between patients, and the oncology community is recognizing the need for these treatments to evolve.

Considerable progress is being made in genotyping to determine if a given regimen is appropriate for a specific tumor. Examples include the identification of human epidermal growth factor receptor 2 (HER2) in the selection of trastuzumab as treatment for breast cancer and tyrosine kinase molecules (RTK) when selecting erlotinib to treat lung cancer or cetuximab to treat metastatic colorectal cancer. These RTK molecules may be either overexpressed or mutated. Inhibition of the defective RTK can aid in the initial complete remission induction and, in some cases, prevention or delay of relapse.

The fundamental — and often over-looked — step is to make the necessary linkages between specific biomarkers and their underlying genotypes, then tailor drug treatment(s) to achieve optimal patient outcomes and minimize adverse reactions.

For example, it was recently discovered that a mutation in the protein phosphatase and tensin homolog (PTEN) has been identified as an important biomarker in many tumors. PTEN is an enzyme that modulates phosphoinositide 3-kinase (PI3K), an enzyme that causes a tumor to grow. PTEN actually inactivates PI3K by removing a phosphate group. Identification
of the PTEN mutation suggests that treating patients with an inhibitor of PI3K can provide what the mutated PTEN cannot do: inhibit tumor growth.

While discoveries such as this are remarkable, it is important to emphasize that there may be more than one mutation, which means that a single therapy may not be curative. Further, the genotype may evolve with new mutations or different genotypes may emerge in different cell lines. Identification of reliable tumor biomarkers can provide an early likelihood of treatment response to a specific drug regimen and/or indicate patient prognosis.

The manner in which clinical trials are currently being conducted is undergoing radical change in an effort to identify appropriate molecular targets. For example, the traditional strategy used in Phase I trials to determine the maximum tolerated dose of a new oncolytic agent is being modified. Pharmacogenomics allows for a genome-wide analysis to identify specific biomarkers in specific tumor types so that targeted, molecular drugs can be developed. Thus, a different approach to clinical trials is evolving to provide the required information for development of both new diagnostics and new therapies. “Umbrella” and “bucket” (also called “basket”) trials are examples of new clinical trial structures designed to enrich the study population with specific tumor-genetic attributes. In this manner, information on the genetic drivers for a specific tumor type may be targeted. Examples of these types of trials include the U.S. Department of Defense BATTLE and NCI MATCH trials. Trials such as these generate huge amounts of information. Special statistical methodologies are being developed to mine these rich data to identify relevant signals appropriate to a specific tumor and a specific patient.

### 2 Safety & Toxicity Profiles Can Be Identified Early

Unfortunately, most chemotherapy drugs have significant toxicities. It is important to identify at-risk patients so that their physician can decide if the expected toxicities are acceptable. For example, will a patient be at a higher risk for side effects like severe mucositis, diarrhea, nausea, and vomiting?

Genomic technology (single-nucleotide polymorphism [SNP] profiling) is evolving as a predictive tool to identify patients who are at risk for these toxicities — prior to treatment. Severe and even fatal toxicities can occur in patients with certain polymorphisms in enzymes that metabolize chemotherapy drugs. A polymorphism is defined as a normal variation in a particular enzymatic gene, usually an SNP, which can lead to modification of its function. Several classic examples of polymorphisms that involve the metabolism of common chemotherapy drugs include 5-flouracil (5FU), Irinotecan and 6-mercaptopurine. Fortunately, polymorphisms that contribute to these toxicities are not common. In the case of 5FU an enzyme, dihydropyrimidine dehydrogenase (DPD) that metabolizes 80% to 90% of 5FU to an inactive form is critical. If DPD is not normally functional or is absent, lethal levels of 5FU can accumulate in the patient. Partial deficiency of this enzyme occurs in 3 to 5% of the population.
In some cases, an enzyme polymorphism may be present that fails the critical activation step of a prodrug; such is the case with clopidogrel. Thirty percent of the population has a mutation in one of the P450 cytochromes, CYP 2C19, required to activate the prodrug. If the patient has this allele, or a mutated form of the enzyme, clopidogrel is not activated. So, in these patients, clopidogrel provides no platelet inhibition to protect from strokes or heart attacks.

Dose targeting is another important advancement in minimizing toxicity and improving efficacy. For example, prior to the initiation of busulfan for stem cell transplant, the patient is given a small test dose of the drug. Blood levels of the drug are then monitored to provide the peak drug level and the rate of drug clearance. From these data an individual patient dose of busulfan can be determined to ensure that treatment efficacy is optimized and toxicity reduced.

3 Early Therapy Response Monitoring Enables Informed Decisions

An additional aspect in genomic applications to cancer diagnosis, classification, treatment, and monitoring is its use in assessing treatment efficacy. Companion diagnostics, the use of medical devices to determine the risks and benefits of a particular therapy to a patient, can be used to monitor a patient’s response to a given therapy. With the information gathered, a physician can make an informed, immediate decision regarding therapy or dosage adjustments.

Take, for example, HER2 in breast cancer and fms-related tyrosine kinase 3 (FLT3) in acute myeloid leukemia. As the tumor is treated, the biomarker abates, and a companion diagnostic tracks the progress. Thus, the rate and extent of successful treatment can be determined. Likewise, the recurrence of the biomarker can indicate recurrence of the cancer. Regardless, faster, more informed, and more personalized treatments are possible with the right information.

4 The Economic Impact is Vast

The impact of pharmacogenomics has critical downstream effects on its implementation not only to the field of hematology and oncology but also to other areas of medicine.

Identification of a regimen that can effectively target a specific molecular defect in a tumor represents, of course, a major medical breakthrough — one that has the potential to positively impact pharmacoeconomics.

First, for any given tumor, pharmacogenomics has the potential to reduce the number of tried-and-failed therapies, reducing the accumulated toxicities from exposure to multiple ineffective regimens, reducing the number of adverse events, and so on. The implications are far-reaching when we’re able to identify the right therapy for the right patient early in treatment.

Additionally, by enriching the treatment population with appropriate patients, and by reducing the size and duration of clinical trials, the path for new drug development and time to market is being accelerated. Specific study subjects are identified and screened to maximize potential efficacy and to exclude patients whose SNP profile may indicate prohibitive serious adverse events (SAEs). All of these aspects are important in risk management during the drug development process.
The ability to improve overall patient outcomes and reduce toxicities while improving the pharmacoeconomic impact of the correct regimen for specific cancers in a particular patient is critical — and now possible. Of course, the expense of developing companion diagnostic tests is still significant, and new approaches to reduce these costs are imperative. SNP analysis, cell surface epitope identification, and tumor micro particle diagnostics all offer real potential to reduce the economic burden of companion diagnostics and enhance outcomes for patients and payers in the future.

5 More Rigorous Caregiver & Payer Education is Possible (& Expected)

A significant barrier to the rapid implementation of pharmacogenomics to all oncology patients derives from the fact that not all hematologists and oncologists are well-versed in the importance of pharmacogenomics. Education for all healthcare providers and students is necessary. Practicing providers may need educational tools provided by pharma and CROs. The encouraging news is that most clinical centers are now adopting genotyping and phenotyping (observing interaction of an organism’s genotype and environment) as a standard of practice.

Success of these new approaches to drug and protocol development in the world of personalized medicine depends on early identification of toxicity and efficacy of treatment. These elements are necessary to avoid more severe toxicity or continuing with a therapy that is ineffective. The patient, payers, and providers all benefit from avoiding ineffective and unnecessarily toxic therapies that, in principle, can be prevented by pharmacogenomics screening.

To capture these emerging data, consistent patient and nurse involvement is essential. The patient must be educated in what is important in their care and treatment regimen, so he or she is able to document and report important events. Clinical trial and marketed product nurses, through physician and patient services, can effectively participate in this process by acquiring, organizing, and communicating relevant information. Nurses, whether onsite or in call centers, are able to obtain and record critical data, which is then brought to the physician’s attention.

The Future of Pharmacogenomics: Oncology & Beyond

Even in these early stages, pharmacogenomics is redefining our approach to new drug development, clinical evaluation of new molecules, diagnosis and classification of cancer diagnosis, treatment regimen selection, and post-treatment monitoring of patients. Further maturation in all of these areas will be important and require continued education at all levels of participation.

REFERENCES:

UBC is changing the face of oncology & we are at the forefront of the pharmacogenomics evolution.