

Precision Medicine: Myth or Reality

Faculty Presenter

Bruce A. Chabner, MD, Allen Distinguished Investigator, Clinical Director Emeritus, Massachusetts General Hospital Cancer Center; Professor, Department of Medicine, Harvard Medical School, Boston, MA, USA

Scholars' Summaries

*Authored by **Olive Eckstein, MD**, Texas Children's Hospital and Baylor College of Medicine, Houston, TX, USA*

The objective of precision medicine is to target a common molecular pathology rather than disease histology in order to optimize outcomes based on specific biologic and genetic findings in an individual.

For the most part, traditional chemotherapy targets DNA synthesis pathways universally shared by normal cells and cancer cells. Due to this imprecise mechanism, response rates to single traditional chemotherapy drugs are typically less than desirable. These drugs also cause damage to DNA in normal cells, which can result in increased risk of secondary malignancy in addition to a plethora of other toxicities.

One of the most important tasks in expanding precision medicine is to find a biomarker that will delineate a distinct population of patients. Once this subgroup of patients has been identified, effective and precise drugs can be developed for this target.

Precision medicine is a relatively new but very promising strategy, and imatinib was one of the first drugs in this era to target a specific fusion protein and successfully improve outcomes for patients with CML and Ph+ ALL in 2001. It has of course been followed by several other successful targeted drug therapies, including ALK inhibitors for ALK positive tumors and BRAF inhibitors for BRAF mutated cancers such as melanoma and Langerhans cell histiocytosis.

Critiques of precision medicine have largely been related to limited resources in terms of cost and universal availability as well as a deficiency in randomized trials. In addition, tumor heterogeneity and clonal evolution present significant challenges for use of single drug targeted therapy. Many drugs are not restricted to a single molecular target, and pharmacokinetics can be quite variable between patients. In addition, individual host variables in immune status and the tumor microenvironment may clarify differences in outcomes analysis of response rates and toxicity profiles of patients with the same molecular biomarker.

As precision medicine continues to improve, pharmacokinetic monitoring will provide individualized dosing. Second and third-generation targeted therapies will improve outcomes with better specificity and affinity, ability to cross the blood-brain barrier, and the capacity to circumvent mutations responsible for drug resistance. Despite these challenges, the principle of precision medicine is to develop targeted drugs which will primarily be restricted to cancer cells, thereby limiting toxicities and increasing response rates to treatment.

*Authored by **Janaki Parameswaran, MD**, Yale New Haven Hospital, New Haven, CT, USA*

In his lecture, Dr. Bruce Chabner discussed precision medicine, which is the management of disease based on its biology and genetics. He explained its uses/limitations, described methods to study drug resistance, and provided examples of how to make drugs more precise. He began by contrasting chemotherapy with targeted agents, and addressing the importance of precision medicine. He discussed its benefits, including increased specificity for targeting cancer vs normal tissues and high

response rates, which can lead to early drug approval by the FDA. Examples of precision medicine in a variety of malignancies were described, and he had an interactive session on how to design “precise” drugs using his research on folate receptors. One folate receptor is only expressed in a few adult tissues, and he asked the STOFF participants to come up with multiple ways to exploit this knowledge to design anti-cancer therapies. A few approaches include antibodies, ADCCs, and T-cell therapy. He concluded by discussing limitations of personalized/precision medicine and ways to address high cost, pharmacokinetic variation, lack of drug specificity, lack of randomized trials to better assess effects on overall survival, and tumor heterogeneity.

The lecturers are now investigating into the novel therapeutic strategy targeting folate transporters, which is highly expressed in tumor cells as well as embryonal tissues, and on a few mature tissues such as apical surface of kidney, intestine, lung, placenta and choroid plexus. As compared with methotrexate, the new drugs for precision medicine targeting folate transporter are described as follows; 1) folate drug-conjugate, 2) genetically-engineered T-cell immunotherapy, 3) complement-mediated tumor cell killing, 4) immune effector cell-mediated antibody-dependent tumor cell killing (ADCP/ADCC), and 5) tumor vaccine targeting the transporter. Remarkably, the soluble folate transporter is a poor prognostic marker for ovarian cancer patients and can be recognized as a novel biomarker.

Biomarkers used to select patients for novel therapeutics have guided patient selection in many successful drug trials in recent years and have led to a profound shift in the process for drug approval. Not only has the use of biomarkers accelerated the pace of cancer drug development but also the discovery of unique genomic subsets of common tumors has changed our basic concept of cancer. No longer are histological categories of major tumors sufficient to define treatment. A variety of tumors derived from different tissues are now recognized as collections of molecular subsets of cancer, with each subset having its own natural history and responsiveness to treatment.

Authored by Go J. Yoshida, MD, PhD, Tokyo Medical and Dental University, Tokyo, Japan

Conventional chemotherapy should be replaced by personalized cancer treatment to enhance the therapeutic effect and reduce side effects in each patient. The term ‘precision’ refers to the prospects for enhanced molecular resolution, mechanistic clarity, and the therapeutic cogency which probably accompany clinical implementation of genomics technologies. The implementation of personalized cancer therapy depends on the genomic tumor testing available, crucial both for the rapid drug development and for clinical practice. However, there is a skeptical view of personalized medicine because of the elevated medical cost, tumor heterogeneity, the demand of genomic analysis, and no survival benefit so far.

Precision medicine requires treatment specific for the molecular pathology with biomarker which defines a unique population and diagnosis based on molecular or immunological analysis of the malignancy in an individual patient. Typical examples of precision medicine include imatinib directly targeting bcr-abl in CML, crizotinib targeting MET/ALK/ROS1 in NSCLC, and vemurafenib targeting mutant BRAF V600E in melanoma. Given that tumor tissues exhibiting even the identical patho-histological subtype can show different responses to the same treatment, molecular pathological diagnosis is mandatory before clinicians perform anti-cancer treatment. For instance, colorectal cancer sometimes has gain-of-functional mutations in RTK (receptor tyrosine kinase) other than BRAF V600E, which is why vemurafenib alone does not show therapeutic effect in such cases. Thus, the combination therapy with HER2 inhibitor trastuzumab and BRAF inhibitor vemurafenib significantly reduces the tumor progression in that case.

Importantly, intra-tumoral heterogeneity and molecular evolution under the selective pressure of chemotherapy makes it challenging to provide cancer patients with personalized medicine. Notably, sequential biopsies would be morbid and impractical, circulating tumor cell analysis is limited in the number of cells available, and circulating DNA is not specific to the tumor site. Therefore, the establishment of the novel biomarker should be warranted.

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Authored by Y. Shrike Zhang, PhD, Harvard Medical School Cambridge, MA, USA

Dr. Bruce Chabner gave a very exciting lecture on precision medicine, which primarily focuses on the use of patient-specific tumor profiles, including, for example, analyses of genomics and biomarkers, to provide personalized anti-cancer drug treatment. Precision medicine allows for tumor biology-specific diagnostics, patient-specific treatment regimens with higher responses and lower side-effects, and cost-effectiveness and timely treatment. One interesting example given was the folate transporter family – the reduced folate carrier, the low pH proton coupled transporter, and the folate receptor – out of which the first two are almost ubiquitously present throughout different tissues in the body and the third one is mainly expressed on the tumorous tissues with only minor presence in a few selected tissue types. Based on this fact, several drug formulations that directly target the folate receptors (e.g. antibodies) or take advantage of specific molecules (e.g. folate antagonist or folic acid) to target the folate receptors have been produced and progressed into different phase trials. Contrarily, precision medicine based on genetic and/or biomarker analyses may not be as precise as we anticipate, since it can be masked or affected by a range of interferences such as multiple targets, variations in pharmacokinetics, drug resistance, tumor context, and even possibly the immune status of the patients. However, these challenges may be overcome, or at least partially overcome, by development of better drugs and methods for tumor analyses and the use of drug combinations.

This topic is of particular interest to me as my goals are exactly aligned with precision medicine – i.e. constructing personalized tumor models that can be used for personalized drug screening, using a bioengineering approach in combination with cancer biology. I believe that, besides purely relying on cancer genomics and biomarkers, a systems biology strategy based on recreating the patient tumor microenvironment in a model platform, in combination with the analyses at the molecular scale, may be helpful in refining precision medicine and may maximize its efficacy in patient-specific cancer treatment.