ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Improving Clinical Trial Design Through Quantitative Pharmacology

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H&O What is quantitative pharmacology?

MM The basic idea behind quantitative pharmacology is that we develop a better understanding of pharmacotherapeutics as we apply greater computing power and more precise, thorough measurement of drug effects in all forms, from laboratory and molecular research to population drug safety studies. More formally, a National Institutes of Health (NIH) Working Group described quantitative and systems pharmacology (QSP) as "an emerging discipline focused on identifying and validating drug targets, understanding existing therapeutics and discovering new ones. The goal of QSP is to understand, in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology. QSP aims to develop formal mathematical and computational models that incorporate data at several temporal and spatial scales; these models will focus on interactions among multiple elements (biomolecules, cells, tissues etc.) as a means to understand and predict therapeutic and toxic effects of drugs. Creation of multi-scale models that ultimately span knowledge of molecules, cells, tissues and patients will be particularly critical for pre-clinical and clinical research teams evaluating target selection and testing therapeutic proof of concept. QSP draws on several existing disciplines, including classic pharmacology, chemical biology, biochemistry and structural biology, molecular genetics and genomics, pathology, applied mathematics, and medicine, and has an intrinsic and extensive experimental component that incorporates approaches from tissue and organ physiology, pharmacology and cell biology as well as bioinformatics and '-omics' approaches."[1]

Arguably, pharmacology has always been a quantitative science. But several factors have recently made it more so: (1) the decreasing costs of collecting and storing data; (2) the improved capacity to use computational modeling to analyze and interpret those data; and (3) the merging of studies of pharmacokinetics and pharmacodynamics with systems biology. The significant impact of these recent developments on the conduct of classical pharmacology has led researchers to refer to the field now as "quantitative pharmacology."

H&O What are some limitations of the traditional approach to drug development and clinical trial design?

MM Exciting developments in science and technology have begun to change how cancer is treated and hold promise for greater advances. However, our progress is constrained because we continue to adhere to conventional methods that no longer serve the cancer research community well.

For example, we are still relying on simple qualitative methods for evaluating the effects of treatment on individual patients and populations. The Response Evaluation Criteria In Solid Tumors (RECIST) relies on measurement of lesions to identify progressive disease, stable disease, partial response, and complete response. As efforts

to develop new oncology drugs for solid tumors first accelerated in the 1970s, a major problem was efficient, reproducible detection and reporting by clinicians of observable effects of treatments on tumor burden. Using crude tools of measurement at that time, the imprecision of clinician assessments was a well-recognized, carefully studied problem.[2] These interclinician inconsistencies in reporting treatment effects were a major challenge to the conduct and interpretation of early- and late-stage clinical trials. Multiple organizations tackled this problem by (1) standardizing the assessment of tumor burden (determining what constitutes a target lesion) and (2) establishing thresholds for change in tumor burden sufficient to report an objective response.[3]

RECIST was a consensus updating of the original standard systems for tumor burden assessment.[4] RECIST incorporated computed tomography (CT) imaging. Because the images could yield a more precise assessment of tumor burden than the conventional methods of the 1970s, these criteria lowered the magnitude-of-tumor-burden change threshold for reporting objective response. RECIST proved inadequate in several settings, including detecting effects of immunotherapy,[5] and detecting effects of other therapies in specific diseases, such as gastrointestinal stromal tumors[6] and glioblastoma multiforme.[7] Researchers in these settings developed modified criteria that better detected treatment effects. However, these criteria still forced conversion of quantitative data—the apparent change in tumor burden for each patient over time—into categorical, qualitative data. The measurement of tumor burden with digital imaging is much more precise and should no longer require these somewhat arbitrary qualitative, categorical systems.[8,9]

The main problem with qualitative, categorical systems of tumor burden assessment is that they are inefficient. For a RECIST-based endpoint, such as response rate or progression-free survival, to demonstrate that a new treatment is superior to a standard treatment requires higher enrollment in a clinical trial than more quantitative methods. Similarly, when clinical trials have enrolled large numbers of patients but only captured the RECIST categories of partial response, stable disease, or progressive disease (in most metastatic solid tumor trials, few patients ever have a complete response), they have limited statistical power that would allow scientists to detect and develop biomarkers as new diagnostics.[10]

H&O How can quantitative pharmacology improve patient outcomes?

MM There are 2 basic areas in which quantitative pharmacology strategies can be helpful. First is to improve the speed and yield of the development of new drugs. Second is to improve the treating physician's ability to evaluate a patient and help him or her make treatment decisions more quickly and effectively than in the past.

H&O What are some examples of the use of quantitative pharmacology in clinical trials?

MM An active area of investigation for years now has been the development of tumor growth–inhibition models.[9] In general, these are computational strategies that collect tumor measurements from patients over time to provide new insights into the growth of metastatic solid tumors. Several groups have developed tumor growth inhibition models in solid tumors such as colorectal cancer, renal cancer, and non–small cell lung cancer. The metric of time to tumor growth has been shown to predict the effects of treatment on overall survival. This metric involves the same measurement used to determine the categorical response in RECIST: tumor burden as shown on computed tomography. However, time to tumor growth is a calculation of the changes in the sum of the longest dimensions of those tumors over time. This measurement generates a more continuous assessment of the tumor's growth rate during the course of treatment. In a clinical trial of patients with colorectal cancer, Claret and colleagues showed that using time to tumor growth as an endpoint could allow studies to enroll fewer patients and to shorten observation periods as compared with conventional trials.[11]

Prostate cancer has been a disease in which it has been especially challenging to characterize tumor burden effectively. Computational approaches have been applied to develop better early measures. Stein and coworkers examined serial prostate-specific antigen (PSA) measurements for patients from 5 completed trials at the National Cancer Institute and demonstrated that a derived estimate of the tumor growth rate better correlated with survival than the more simply calculated PSA-doubling time.[12] Meanwhile, more quantitative analytical approaches to conventional bone imaging of metastatic prostate cancer have also enabled better detection of treatment effects.[13] Recognizing the importance of more quantitative approaches, Scher and colleagues leveraged recently completed international phase 3 trials to better develop quantitative biomarkers.[14] This group demonstrated that combined analysis of changes in circulating tumor cell counts and lactate dehydrogenase by 12 weeks of salvage therapy in metastatic castration-resistant prostate cancer could serve as a surrogate for 2-year survival in individual patients. Prospective validation studies in this setting are ongoing. If validated, regulatory authorities will have to consider enabling these quantitative measures to serve as endpoints, instead of overall survival, in prospective

clinical trials. In addition, given the individual patient-level surrogacy, clinicians would begin to incorporate these same measures into individual treatment decisions.

H&O What are the barriers to using quantitative pharmacology to improve clinical trial design?

MM One barrier is the concern from trial sponsors and investigators that the use of novel quantitative endpoints will face regulatory obstacles. There is a tendency to be conservative and to rely on the older methods previously used to obtain new drug approvals.

Another barrier is the operational complexities. The accurate collection of data continues to be a challenge for investigators and sponsors. Studies that employ unvalidated markers often assess a large number of variables for each patient. It is hoped that the collection of these data will ultimately allow more efficient execution of clinical trials. In the short-term, however, the need to ensure that all of the data are collected at the right times and with accurate documentation is somewhat burdensome for all involved, including patients and investigators.

H&O Do you anticipate that the use of quantitative pharmacology will evolve in any way?

MM In the near future, once the basic obstacles are overcome, I expect to see the routine use of quantitative data as clinical trial endpoints, as well as in routine care. This will happen to the point where the term "quantitative pharmacology" is no longer used but will be encompassed by routine cancer care.

Disclosures

Dr Maitland is a principal investigator of the Computational Modeling of Tumor Burden by CT to Advance Cancer Therapeutics project (grant R01CA194783); an investigator on the Foundation for the NIH Biomarkers Consortium project VoICT-PACT: Volumetric CT, Improving Metrics for Phase II Analysis of Clinical Trial Results (CSC); and an ad hoc consultant to the US Food and Drug Administration Oncology Drug Advisory Committee.

References

1. Sorger PK, Allerheiligen SRB. Quantitative and systems pharmacology in the post-genomic era: new approaches to discovering drugs and understanding therapeutic mechanisms. National Institute of General Medical Sciences website. https://www.nigms.nih.gov/training/documents/systemspharmawpsorger2011.pdf. Posted October 2011. Accessed July 12, 2016.

2. Moertel CG, Hanley JA. The effect of measuring error on the results of therapeutic trials in advanced cancer. *Cancer*. 1976;38(1):388-394.

3. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47(1):207-214.

4. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205-216.

5. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420.

6. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol*. 2007;25(13):1753-1759.

7. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28(11):1963-1972.

8. Sharma MR, Maitland ML, Ratain MJ. RECIST: no longer the sharpest tool in the oncology clinical trials toolbox—point. *Cancer Res*. 2012;72(20):5145-5149.

9. Maitland ML, Schwartz LH, Ratain MJ. Time to tumor growth: a model end point and new metric system for oncology clinical trials. *J Clin Oncol*. 2013;31(17):2070-2072.

10. Wheeler HE, Maitland ML, Dolan ME, Cox NJ, Ratain MJ. Cancer pharmacogenomics: strategies and challenges. *Nat Rev Genet*. 2013;14(1):23-34.

11. Claret L, Gupta M, Han K, et al. Evaluation of tumor-size response metrics to predict overall survival in Western and Chinese patients with first-line metastatic colorectal cancer. *J Clin Oncol*. 2013;31(17):2110-2114.

12. Stein WD, Gulley JL, Schlom J, et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. *Clin Cancer Res*. 2011;17(4):907-917.

13. Anand A, Morris MJ, Kaboteh R, et al. Analytic validation of the automated bone scan index as an imaging biomarker to standardize quantitative changes in bone scans of patients with metastatic prostate cancer. *J Nucl Med*. 2016;57(1):41-45.

14. Scher HI, Heller G, Molina A, et al. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2015;33(12):1348-1355.