

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Bayesian Approaches to Evaluating Doses of Drugs



Gary L. Rosner, ScD
Eli Kennerly Marshall Jr. Professor
Director, Research Program in Quantitative Sciences
and Division of Oncology Biostatistics & Bioinformatics
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland

H&O What is Bayes' theorem?

GR Bayes' theorem is a rule in mathematical probability for computing the probability of an event given that something else is true—that is, a conditional probability. In medicine, these events might include the result of a diagnostic test, the presence of a disease, the effectiveness of a treatment, or the occurrence of adverse side effects if a patient receives a particular treatment. Probability theory rests on axioms to create a coherent system for calculating probabilities. Conditional probability refers to the likelihood that something is the case or that an event will occur based on other knowledge. An example of a conditional probability is the probability that a patient has a disease when a diagnostic test result is positive. Bayes' theorem indicates how to go from the probability that a test is positive, given that the patient has the disease, to the probability that the patient has the disease, conditional on the test being positive for the disease. Why do we need to know how to transform the probability? When a new test for diagnosing a disease is in development, the investigators apply the test to subjects known to have the disease (ie, already diagnosed by means of a standard diagnostic method) and to individuals who are disease-free. Investigators use these data to determine the probability of a positive test result, given the presence of the disease, which is called the test's sensitivity. Similarly, they use the data to estimate the test's specificity, which is the probability of a negative test result, given absence of the disease. These probabilities arise because the tests are not perfect. When a diagnostic test is positive, the patient wants to know if

he or she does in fact have the disease. Because the test is not perfect, we need a way to convert the test's sensitivity and specificity probabilities to statements about the likelihood that the patient has the disease. That is where Bayes' theorem comes in.

Bayesian inference derives its name from Bayes' theorem. This approach to statistical inference uses Bayes' theorem to update current knowledge in light of new evidence. For example, a physician who is uncertain of how well a treatment will work in a particular patient can consult data from studies of that treatment in a group of similar patients, and use the information to update his or her certainty or prediction about the benefit. Bayesian inference allows one to condition on observations to make inferences about treatment effects.

H&O Can you please describe Bayesian models?

GR A Bayesian model typically begins with a mathematical characterization of uncertainty or belief about something. In a clinical trial setting, that uncertainty may relate to whether a new treatment is superior to the current standard of care. It is necessary to use some type of mathematical probability function to characterize the heterogeneity that is seen across patients who are participating in a clinical trial. Bayes' rule shows how to combine the prior probability about the new treatment's efficacy—which is the uncertainty that exists before the study—with the study data to calculate updated probabilities for making inferences about the treatment's efficacy, given the new data. The models used for inference incorporate probability distributions.

H&O How can Bayesian models and calculations be incorporated into clinical trial design?

GR Many phase 1 studies already incorporate Bayesian calculations and models. The continual reassessment method incorporates an underlying model about the rela-

A key advantage to the Bayesian approach is that it can measure the certainty that there was a difference between treatments.

tionship between dose and the risk of adverse events. As patients are treated at different doses, observations can be used to update knowledge about the risk of adverse events at a given dose. The decision about whether to treat a new patient with the same dose, to escalate to a higher dose, or to stop the study is based on Bayesian calculations in many phase 1 trials.

In phase 2 trials, Bayesian models and calculations are used in several ways. Uncertainty may still exist about the optimal dose of a drug after a phase 1 study, particularly one that focused exclusively on toxicity. A phase 2 trial may compare different doses of a drug or ways of combining the drug with other therapies. This trial may use Bayesian calculations along the way. The study may adapt treatment assignments as patients enter the study, meaning that data concerning the clinical effect or the risk of toxicity associated with different treatments are used to preferentially assign patients to those treatments that appear more effective and/or less toxic. Subsequent patients then have a higher probability of receiving the better treatment in the study. The goal is to increase the proportion of patients who receive the better therapies while also learning about these therapies.

Trials with a seamless design transition from phase 1 to phase 2 by eliminating certain doses as the study progresses. These trials might also randomly assign patients to the standard of care, which acts as a control arm, while determining the optimal dose of a new drug. With a Bayesian approach, it is also easy to incorporate historical data from studies of the standard-of-care treatment. With the Bayesian approach to statistical inference, as

more information is gathered, it can be used to update the degree of certainty or knowledge. Historical information can be incorporated into the characterization of prior uncertainty.

Many phase 2 studies evaluate a set dose drawn from a phase 1 study, even though this dose may not be optimal for several reasons. In our studies, my colleagues and I incorporate continual monitoring of adverse events and use Bayesian calculations to estimate the risk of an adverse event when treating the next patient. If we become certain that the risk is too great, we will consider stopping the study. We also use Bayesian calculations for interim monitoring, to see whether the available data provide enough evidence to conclude that one treatment is superior to the other or that the trial is unlikely to generate sufficient evidence to allow conclusions regarding treatment differences if it continues as planned. In the latter case, the trial may be stopped for futility.

In oncology, many studies now incorporate biomarkers to evaluate treatment or predict outcome. It may be possible to use genetic predisposition or molecular characterization of a tumor to predict whether patients will develop a certain toxicity associated with a drug. The enrollment criteria might exclude patients at higher risk of toxicity and preferentially enroll patients who have a higher chance of a good outcome. These determinations will involve Bayesian calculations.

Phase 3 trials can use Bayesian calculations for monitoring toxicity and efficacy throughout the study. A study might be stopped based on a difference in outcomes among treatment arms or because no such difference is expected. Phase 3 trials may also incorporate adaptive, outcome-informed randomization.

H&O What advantages do Bayesian models provide over other models?

GR An alternative strategy is the frequentist approach, which involves proof by contradiction. The frequentist approach uses a *P* value, which in a clinical trial describes the likelihood that one would observe the same or more extreme treatment differences when the treatments are equally effective. A smaller *P* value corresponds to a lower probability that one would observe very different treatment-specific outcomes in the absence of a treatment difference. In contrast, the Bayesian approach provides a probability value to the statement that there is or is not a difference between the treatments in light of the study data. The frequentist approach does not provide this probability.

A key advantage to the Bayesian approach is that it can measure the certainty that there was a difference between treatments. It is possible to incorporate that

information in a way that is consistent with mathematical probability. The Bayesian approach also provides a more straightforward way to incorporate results from other studies into inferences for the current study.

Physicians are always making decisions for patients, and decision-making under uncertainty is best handled using Bayesian calculations. The Bayes decision rule is optimal in the sense that it maximizes the expected or average trade-off between benefits and costs.

H&O How can Bayesian models be used to assess lower dosages of marketed drugs?

GR The Bayesian approach allows incorporation of historical information to predict how a treatment will perform. For the marketed drug, there is experience in how the drug performs at certain doses. It is possible to incorporate that information into a study's design, and thereby reduce the sample size when comparing a lower dose with higher doses. A smaller trial would allow us to find an answer more efficiently in a less resource-intensive way.

H&O Is there an example in which a Bayesian model was used to assess lower dosages of a marketed drug in oncology?

GR I am not aware of specific examples in oncology yet that incorporate Bayesian calculations. I am currently designing a study that will use a Bayesian approach. There are examples in other diseases, such as diabetes and Alzheimer disease. A study of dulaglutide (Trulicity, Lilly) followed an adaptive, randomized design in patients with diabetes to evaluate different doses during a phase 2 portion. It selected the best doses based on Bayesian calculations, and continued as a randomized, controlled clinical trial with an active comparator.

H&O Does the use of the Bayesian model impact the interpretation of data?

GR The Bayesian model affects the interpretation of the inference from the data. As a Bayesian will always say, the data are the data. We condition on what we observe, as opposed to a frequentist, who conditions on an hypothesis. The Bayesian model affects our interpretation of the outcome of an experiment in that we can make a direct statement about the probability of certain scenarios, such as the probability that the patient will live longer than 3 years when treated with a drug or that a patient will do better on drug A vs drug B. A Bayesian model can quantify these probabilities, incorporating all uncertainties based on the heterogeneity among patients and other studies.

H&O Can a physician use a Bayesian approach to lower a dose for a particular patient?

GR In some sense, physicians already do. We all use Bayesian inference every time we make a decision by using what we know from experience and determining the risk. We may ignore the risk, but we tend to update our assessment of risk as we gain experience. A patient might report adverse events during treatment, and the physician, based on his or her experience treating other patients, may modify the regimen or continue treatment as is. Physicians use their knowledge drawn from experience with other patients to guide decision-making and tailor their approach for a particular patient.

H&O Are there any new ways of using Bayesian models in drug development?

GR Many drug developers are interested in applying outcome adaptive randomization. With this approach, patients are randomly assigned to one of many treatments, and after the study has treated a certain number of patients, the randomization may change to favor treatments associated with better outcomes. Subsequent patients will therefore have a higher probability of receiving treatments that appear superior. As time progresses, those probabilities will change. If the data suggest that a particular treatment is superior with a high degree of certainty, then the study may stop.

Newer studies are also incorporating historical information from past studies. Bayesian methods are being used in meta-analyses, in which the results from many completed studies are used to make inferences about how treatments compare. There is interest in using Bayesian methods for studies of rare diseases or studies in children, which will typically have a small sample size. In smaller studies, it is necessary to leverage as much information as possible from each observation and all available sources of relevant information.

H&O Are there any other innovations in trial design?

GR There are studies in oncology that aim to match treatments to patients, based on the molecular characterization of their tumors. Many newer anticancer treatments have been designed to affect cancer cells that have a particular molecular aberration and to disrupt pathways for cancer cells while sparing normal cells. It is hoped that these targeted agents will have less toxicity. Sometimes the agents have other effects, good or bad, beyond the intended one. There are several studies that use molecular characterization to match patients to targeted therapies,

while recognizing that there may be other agents that would be equally effective or that the targeted agent may also be effective for patients who exhibit different molecular characterizations. This approach is being used in the I-SPY 2 trial (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2) in breast cancer and the BATTLE studies (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) in non-small cell lung cancer, as well as in the MATCH study (Molecular Analysis for Therapy Choice) from the National Cancer Institute, which has screened thousands of patients with advanced or refractory solid tumors, lymphoma, or myeloma. Some of the new studies are using Bayesian calculations to determine which treatment to give to subsequent patients, based on previous data gathered in the study, such as experience with patients who have similar molecular characteristics.

Disclosure

Dr Rosner is a member of an independent safety monitoring committee for a study sponsored by Novartis. He owns stock in Johnson & Johnson.

Suggested Readings

- Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5(1):27-36.
- Berry DA. Decision analysis and Bayesian methods in clinical trials. *Cancer Treat Res*. 1995;75:125-154.
- Campbell JI, Yau C, Krass P, et al. Comparison of residual cancer burden, American Joint Committee on Cancer staging and pathologic complete response in breast cancer after neoadjuvant chemotherapy: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). *Breast Cancer Res Treat*. 2017;165(1):181-191.
- Cunanan KM, Gonen M, Shen R, et al. Basket trials in oncology: a trade-off between complexity and efficiency. *J Clin Oncol*. 2017;35(3):271-273.
- Ding M, Rosner GL, Müller P. Bayesian optimal design for phase II screening trials. *Biometrics*. 2008;64(3):886-894.
- Gault LM, Lenz RA, Ritchie CW, et al. ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. *Alzheimers Res Ther*. 2016;8(1):44.
- Geiger MJ, Skrivaneck Z, Gaydos B, Chien J, Berry S, Berry D. An adaptive, dose-finding, seamless phase 2/3 study of a long-acting glucagon-like peptide-1 analog (dulaglutide): trial design and baseline characteristics. *J Diabetes Sci Technol*. 2012;6(6):1319-1327.
- Harris L, Chen A, O'Dwyer P, et al. Update on the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH/EAY131) precision medicine trial. Presented at: the 2017 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; October 26-30, 2017; Philadelphia PA. Abstract B080.
- Hee SW, Hamborg T, Day S, et al. Decision-theoretic designs for small trials and pilot studies: a review. *Stat Methods Med Res*. 2016;25(3):1022-1038.
- Ivanova A, Rosner GL, Marchenko O, Parke T, Perevozskaya I, Wang Y. Advances in statistical approaches oncology drug development. *Ther Innov Regul Sci*. 2014;48(1):81-89.
- Kim ES, Herbst RS, Wistuba II, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov*. 2011;1(1):44-53.
- Skrivaneck Z, Gaydos BL, Chien JY, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). *Diabetes Obes Metab*. 2014;16(8):748-756.
- Trippa L, Rosner GL, Müller P. Bayesian enrichment strategies for randomized discontinuation trials. *Biometrics*. 2012;68(1):203-211.
- Zhou X, Liu S, Kim ES, Herbst RS, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer—a step toward personalized medicine. *Clin Trials*. 2008;5(3):181-193.