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STATISTICIANS DEVELOP NEW TWO-CYCLE DOSE-FINDING METHOD FOR PERSONALIZED CANCER TREATMENTS

SEATTLE, WA, AUGUST 10, 2015 – A new technique developed by statisticians that is helping doctors optimize the dose of a new cancer treatment patients receive in phase I/ II clinical trials was presented today by Juhee Lee, assistant professor of applied mathematics and statistics at the University of California, Santa Cruz, during a session at the 2015 Joint Statistical Meetings (JSM 2015) in Seattle.

During a session titled Bayesian Dose-Finding in Two Treatment Cycles Based on the Joint Utility of Efficacy and Toxicity, Lee presented the "Optimal Two-Cycle Dose-Finding Design" she developed in collaboration with Peter F. Thall, professor of biostatistics at The University of Texas MD Anderson Cancer Center in Houston; Peter Mueller, professor of mathematics at The University of Texas at Austin; and Yuan Ji, director of the Program for Computational Genomics and Medicine Research Institute at NorthShore University Health System in Chicago.

When a promising new experimental anticancer treatment is developed, the only way to determine how it affects humans is to use it to treat actual cancer patients. To establish an optimal dose, a phase I/II clinical trial is conducted, during which a sequence of small cohorts of two to three patients are given varying doses of the experimental treatment. When the clinical outcomes of each cohort are observed, their data are added to the accumulated dose-outcome data from all previous patients and this data is used to choose the best dose for the next cohort. When the phase I/II trial is completed, the final best dose is selected to treat future patients.

Although the notion of dose-finding assumes there is a single dose administered to each patient, this is not always the case in reality. "Medical treatment often involves multiple cycles of therapy. Physicians routinely choose a patient's treatment in each cycle adaptively based on the patient's history of treatments and clinical outcomes. In such settings, a patient's therapy is not one treatment, but rather a sequence of treatments that each is chosen using an adaptive algorithm of the general form 'observe, treat, observe, treat, and so forth,'" explained Lee.

Most clinical trial designs do not account for the multi-stage treatment regimens used by the physicians who treat patients during the trial. Instead, conventional trial designs consider only the initial treatments—as if each patient's outcomes are due to the first cycle of treatment—and disregard the treatment given to the patient in the second cycle.

In a dose-finding trial, each new patient's first dose—given in cycle 1 of treatment—is chosen using so-called "adaptive" rules based on results that have been observed in earlier trial patients. In conventional designs, the rules disregard the patient's cycle 1 dose and outcomes when they choose the patient's cycle 2 dose. As a result, the physician must choose each patient's cycle 2 dose informally, based on his or her intuition. Unfortunately, when making treatment decisions in multiple stages, using intuition can lead to bad decision-making by even highly experienced physicians.

The Optimal Two-Cycle Dose-Finding Design was motivated by this problem, which is experienced frequently in early-phase clinical trials of potential new anticancer agents. Phase I/II trials establish each new patient's dose based on good outcomes—called "treatment efficacy"—such as tumor shrinkage as well as bad outcomes such as "toxicity."

This new dose-finding design is the first to deal with the problem of optimizing each patient's dose levels in two cycles in phase I/II cancer clinical trials. Extensive computer simulations have shown the two-cycle design often is 30% to 35% better than conventional methods in terms of how well it performs in choosing the best dose levels for patients.

Lee presented an example of how the two-stage design might work in practice. In a trial of five dose levels, suppose during the trial a patient is given dose level 4 in cycle 1 and their outcome is toxicity either with or without tumor shrinkage. The optimal two-cycle design would give that patient dose level 4 again in cycle 2, where the true probability of response is 65%. But due to the toxicity seen in cycle 1, a conventional trial design would de-escalate to a lower dose level—1, 2 or 3—for cycle 2, where the response probabilities are 20% to 45%, thus greatly reducing the chance the patient will achieve tumor shrinkage in cycle 2.

The Optimal Two-Cycle Dose-Finding Design is an example of "personalized medicine," because it uses each patient's cycle 1 data to help set a dose level to give that patient in the second cycle of treatment. The design is "adaptive" in two ways, since it also uses the dose-outcome data from other patients participating in the trial. The approach also can be used for dose-finding trials focused on diseases other than cancer, including rapid treatment of stroke or optimizing successive doses of a drug to control pain following surgery, said Lee.

The ultimate goal of the new design methodology is to improve patient benefit by increasing the probability their cancer will be brought into remission while also controlling the risk of toxicity. This goal applies to the patients enrolled in the trial and future patients once the trial is completed and an optimal dose has been established, said Lee.

JSM 2015 is being held August 8–13 at the Washington State Convention Center in Seattle. More than 6,000 statisticians—representing academia, business and industry, as well as national, state and local governments—from numerous countries are attending North America's largest statistical science gathering.

About JSM 2015

JSM, which has been held annually since 1974, is being conducted jointly this year by the American Statistical Association, International Biometric Society (ENAR and WNAR), Institute of Mathematical Statistics, Statistical Society of Canada, International Chinese Statistical Association, International Indian Statistical Association, Korean International Statistical Society, International Society for Bayesian Analysis, Royal Statistical Society, and International Statistical Institute. JSM activities include oral presentations, panel sessions, poster presentations, professional development courses, an exhibit hall, a career service, society and section business meetings, committee meetings, social activities and networking opportunities. Click here for more information about JSM 2015.

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