Cancer Clinical Investigators Should Converge with Pharmacometricians

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The applied quantitative science pharmacometrics has significantly enhanced cancer therapeutics development. Pharmacometrics is now improving our understanding of complex diagnostics. Through the concept of convergence and methods of quantitative and systems pharmacology, pharmacometrics is poised to interconnect mathematical models of disease and therapy to advance cancer care.

See related article by Colomban et al., p. 5342

In this issue of *Clinical Cancer Research*, Colomban and colleagues report a new computational technique to predict survival for patients with metastatic ovarian cancer during initial systemic platinum-based therapy (1). Early changes in the serum tumor marker, CA-125, have been studied to predict clinical outcomes for 35 years (2). This integrated clinical–computational article represents progress, not only for future ovarian cancer investigations, but also highlights a critical cultural advance for the cancer research community. In this case, a gynecologic oncology team has collaborated for several years with experts in an underrecognized applied research field, called pharmacometrics.

Pharmacometrics is the science that quantifies drug, disease, and trial information to aid efficient drug development and regulatory decisions. Increasingly, this science is being applied to optimize drug treatment for individual patients and to advance our understanding of risk factors that dictate variability in response to therapy (3). Just as clinicians have distinct specialties focused on specific diseases and particular skills to apply to patient care, computational scientists have familiarity with specific methods and tools to analyze and interpret data. Historically, clinical research analyses pivoted around answering a binary question (yes or no) pertaining to differentiating responses between two groups of patients, for example control versus new treatment, or sensitive versus resistant. Pharmacometrics provides a quantitative approach to optimize the drug, dose, or regimen for a patient based on risk factors, baseline measurements, and known relationships between intermediary biomarkers and clinical outcomes. This approach takes not only the mean, but the variability into account. Pharmacometrics investigators also characterize relationships between drug concentrations, drug targets, and the consequent effects of drugs engaging their targets. Through collecting just a few informative measurements, from each patient in a large group, the full temporal pattern for an individual patient can be predicted. Increasingly, pharmacometricians have developed new applications for these population modeling techniques, for example the study of changes in solid tumor measurements on CT imaging studies and on robust circulating tumor markers like CA-125.

Most of this work has been performed outside the mainstream of academic medicine and cancer biology research, within pharmaceutical companies, consulting firms, regulatory agencies, and schools of pharmacy. But in 2011, leaders from this field joined NIH leadership, and the academic founders of the field of Systems Biology to conduct workshops and publish a white paper, “Quantitative and Systems Pharmacology in the Postgenomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms.” (4) The leadership of this journal’s parent organization, American Association of Cancer Research, recently promoted the concept of “convergence—the coalescence of diverse scientific disciplines such as engineering, mathematics, physics, and data science to solve cancer mysteries.” Pharmacometrics is the epitome of convergence. Over the last several decades a community of scientists has worked at the interface of computational science and clinical pharmacology, prominently in oncology. This emergence of pharmacometrics and quantitative and systems pharmacology holds significant promise to advance cancer therapy.

Ovarian cancer is the most lethal gynecologic cancer in the United States. The vast majority of patients present with advanced-stage disease. Although response rates to initial therapy are as high as 75%, most patients will unfortunately ultimately relapse and develop chemotherapy-refractory disease. MUC16 is a glycoprotein that is overexpressed on the cell surface of 80% of ovarian cancers and up to 95% of patients with advanced disease. CA-125 is the large domain of MUC16 that is cleaved and released into circulation. It has been readily detectable and robustly quantifiable in basic, standardized laboratory immunoassays and applied to various elements of ovarian cancer care. Repeatedly, researchers have envisioned serum CA-125–derived metrics would become sound predictors to improve ovarian cancer care outcomes, but repeatedly, the results have disappointed. Simple metrics such as sustained 50% decline in CA-125 from baseline, the Gynecologic Cancer Intergroup criteria, have facilitated enrollment of patients in clinical trials, but no single metric has ever become truly useful to inform individual decisions in clinic or to redesign clinical trial endpoints.

The Colomban and colleagues team has published a series of studies devoted to advancing our understanding of changes in the...
serum glycoprotein, CA-125 and treatment outcomes. They first developed a pharmacometric model of temporal changes during initial platinum-based chemotherapy. The primary motivation for their work was to be able to interpolate the pattern of change in CA-125 early in the course of treatment as a predictor of the ultimate impact of treatment on survival. This is not a new idea! In 1996, Buller and colleagues found among 126 patients that "the slope of the CA-125 exponential regression curve is the single most important prognosticator of survival for the patient with ovarian cancer. Treatment algorithms based on this slope may be helpful in developing novel cost-effective clinical trials." (5) The high variance among patients in baseline CA-125 measurements, the timepoints at which subsequent measurements were collected, and the specific patterns of change have made simple metrics ineffective. Meanwhile, more computationally intensive methods have been too complex or just inaccessible to clinical trialists and practitioners. The prior work of this clinical and pharmacometrics team evolved the parameter KELIM, a summary metric of the time course of CA-125 decline (similar to Buller and colleagues slope of the CA-125 exponential regression curve) as a strong predictor of overall survival (OS) that can be calculated after 100 days of initial chemotherapy.

In this article, the clinicians on this team facilitated access to the largest dataset to date of patients with ovarian cancer in first-line platinum therapy with more than 2,700 patients from multiple randomized clinical trials. Dividing the data into development and validation sets, they show consistent association between CA-125 KELIM and OS. The authors have made the software tool that generates the KELIM and OS estimates for an individual patient publicly available at http://www.biomarker-kinetics.org/CA-125, facilitating use of this tool by investigators without a pharmacometrics background. This work opens the door to more quantitatively oriented studies of other ovarian cancer patient datasets. This development of KELIM for CA-125 is an important broader reaching step. In the spirit of Buller and colleagues, the study by Colomban and colleagues explains how KELIM can now be applied...
to better stratify patients with ovarian cancer in future clinical trials. But beyond the immediate clinical trials implications, a key element of quantitative and systems pharmacology is to interconnect related, but independently developed mathematical models (Fig. 1), into multi-scale models. This method of “tying together” our scientific understandings at the population and molecular levels, quantitatively, promises better predictions and more rapid advances—convergence. For example, previously published mathematical models (6) included a $K_{ELIM}$ parameter that was assumed rather than measured and calculated. In this setting Hori and Gambhir employed their calculations to inform use of blood biomarkers in screening for early detection of ovarian cancer.

With collaborating teams, the models that describe the relationships among tumor and healthy tissue release of CA-125 into plasma, the effects of therapeutic interventions on CA-125 measurements and survival of patients can be improved. Ultimately, measurements in a cell/tissue model, animal model, or small group of patients, could be used reliably to estimate the potential impact of a specific treatment on disease in a population (7). This multi-scale, quantitative approach might also clarify some new mysteries in treatment of ovarian cancer. For example, the retained surface portion of the MUC16 glycoprotein is the target for chimeric antigen receptor T cells and antibody-drug conjugates in current phase I trials in patients with recurrent ovarian cancer. These approaches are still experimental with uncertain OS benefit. The changes in CA-125 observed early in the course of treatment will likely be different from those observed in patients receiving first-line platinum-based therapy. But by incorporating our prior knowledge of CA-125 dynamics from multi-scale modeling we could better ascertain how to manage the care of patients with ovarian cancer in this unprecedented care setting.

The rigorous peer review of projects like this represents a new challenge for publishers. As the multidisciplinary nature of these projects requires input from multiple areas of expertise, innovative projects can become nearly peerless. So editors, staff, and societies that support the journals are beginning to innovate new methods and to cultivate pools of reviewers to ensure fairness and discriminate from among exciting reports the likely spurious from those with potential lasting impact. Clinical Cancer Research welcomes manuscripts within cancer-related quantitative and systems pharmacology and has been pleased to evaluate and feature this report from Colomban and colleagues.

Disclosure of Potential Conflicts of Interest

M.L. Maitland has an immediate family member (spouse) who serves as a consultant/advisory board member for Acceleron Pharma, Bayer, Inc., Complex, Inc., Merck, Sharp, and Dohme, Reata Pharmaceuticals, and United Therapeutics. R.E. O’Cearbhaill is a consultant/advisory board member for Tesaro, Clovis, and GlaxoSmithKline. No potential conflicts of interest were disclosed by the other author.

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References

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