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Molecular Therapy

Mathematical Modeling in Immunotherapy of Cancer: Personalizing Clinical Trials

Despite the massive resources currently invested in medical research and development, the rate of entry of new drugs into the market is decreasing. The present system of clinical trials may put too many hurdles in the way of drug development—particularly those targeting cancer, for which the prevalent format of clinical trials was developed long ago mostly to test small molecules. Although the format has been adapted to some protein therapeutics, it is clearly inadequate for the recent, more complex biological treatments. Hence, for these new approaches to help patients, clinical trials must become more innovative and substantially streamlined. This concern has brought up the idea of information technology–mediated trials ("e-trials") that could broaden the patient base.[1] Another idea is that of virtual research and development, using computer simulations of the human body intended to replace the laborious efficacy testing in real humans and reduce the likelihood of drug failure.[2]

Although the recent advent of cell-based prescription immune treatments—e.g., cytokine interleukin 2 (Proleukin®, Prometheus Laboratories, San Diego, CA; for metastatic melanoma and renal cell carcinoma) and antigen-presenting cells sipuleucel-T (Provenge®, Dendreon, Seattle, WA; for metastatic, castration resistant metastatic prostate cancer)—may be heralding the coming of age for cancer immunotherapy, such treatments still illustrate the inadequacy of the current trial design. In part, this is because immunotherapy may allow patients to "live with rather than die from" their tumor—effects that are difficult to capture in conventional short-term response studies. In addition, the clinical success—even of the most effective immunotherapy—is still too unpredictable and sporadic. Unlike the more established treatments that target cancer cells directly, immunotherapy is indirect because it affects cancer by manipulating immunity; hence, variability in the cancer and the induced immune response may both influence outcome. For this reason, enhancing the efficacy of immunotherapy requires answers to why immune surveillance failed, what the hallmarks of effective immunity are, and how to restore immunity to the effective level. The very unpredictability of individual response to a particular immune treatment indicates that the answers will be particular to the individual patient. Inevitably, then, efficacious immunotherapy requires treatment personalization, a goal unlikely to be achieved by traditional empirical approaches to drug development.

Successful immunotherapy should control the dynamic interactions of intrinsic immunity, the tumor, and the immune agent, leading to a therapeutic response. In other words, for rational immune treatment one needs insight into the individual parameters determining the coevolution of the particular immune system, the particular tumor, and the particular immune therapy. This formidable task requires a systemic analysis of complex interacting biological processes within the individual patient. This is beyond the limits of standard preclinical and clinical development; it calls for a paradigm change in clinical trials of immunotherapy.

Mathematical models—whose role is to describe, quantify, and predict multifaceted behavior—can disentangle complex systems, such as mutually interacting immunity, tumor growth, and immunotherapy. The models are simply hypotheses about systems dynamics, "verbalized" by the succinct formal language of mathematics. Formal description renders the models analytically tractable by the plethora of mathematical methods, yielding solutions that embody the system's behavior under given initial conditions. Mathematical models can be tested against relevant clinical information; when additional information about the system becomes available, the model can be refined and adjusted accordingly.

Many mathematical models have been developed over the past 40 years to shed light on cancer progression, to guide refinement of cancer therapy regimens, and to streamline drug development. However, it is only recently that clinical, pharmaceutical, and regulatory bodies have become more attentive to insights drawn from computational sciences, leading to increased consideration by regulatory authorities of computational methods as a means to direct clinical trials of newly developed drugs.[3] Examples of such methods are

statistics-based pharmacometric models, which can pinpoint variables influencing drug pharmacokinetics and pharmacodynamics; such models have already proven pivotal in regulatory decisions.[4] Another example is the "virtual patient," which comprises validated mathematical models of key physiological and pathological processes; this technology has facilitated personalization of drug-administration schedules and resulted in not only stabilization of disease progression but also increased survival and quality of life of a patient suffering from mesenchymal chondrosarcoma and treated with bevacizumab and docetaxel.[5]

In view of the critical need for personalization of treatment, the essential question is whether mathematical models can predict the effects of immunotherapy in a single patient. To study this question, a simple general mathematical model was developed to describe the basic time-dependent relationships of cancer, immunity, and immunotherapy. Thereafter, clinical data from each individual patient, which had been collected before treatment and during its early stages, were employed to evaluate the patient-specific parameters of pharmacokinetics, pharmacodynamics, and cell kinetics. The patient's parameters were then input into the previously constructed general model, turning it into a personalized model. The latter model was then used to simulate the effects of different doses and delivery schedules so that a modified treatment could be selected and applied with the expectation of more effective clinical outcome while the patient was still in treatment. The method was retrospectively applied to a phase II clinical study of therapeutic vaccination for disseminated prostate cancer,[6] using only patient data collected before and early in treatment, and found to predict the late clinical effects.[7]

The initial success of mathematical modeling in immunotherapy indicates that the approach may accelerate the entry of immunotherapy into the mainstream of cancer treatment. Reaching this goal will be greatly facilitated by clinical studies designed with the collaboration of mathematicians, basic and translational scientists, and clinicians. Fortunately, the new generation of scientifically trained physicians entering medical practice and the expanding use of high technology in diagnostics and treatment opens the gate for mathematicians to enter the realm of clinical trials. But this is not sufficient. To permit clinical trials of personalized schedules ("P-trials"), regulatory authorities should allow the replacement of established methodology (testing the response of a patient population to one dosing schedule) with personalized dosing schedules within a restricted range; for example, model simulations have suggested that the increase of vaccine dose up to threefold and administering it once per week, or per two weeks, could stabilize the disease in all otherwise progressing patients (cf. ref. 6). Within the allowed range, the selection of the precise individual regimen will be left to the discretion of the clinician on the basis of model predictions and considering the particular patient's status. This will hopefully lead to improved individual response and hence to more significant results of clinical trials of new immunotherapy modalities.

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