Editorial

Shaping the AML Treatment Landscape—Modeling a Path through Plenty, Uncertainty, and Paucity

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Introduction

The last two decades have identified and characterized heterogeneities arising in the genetic structure of the bone marrow malignancy, acute myeloid leukemia (AML), to partly explain the variation in outcomes among similarly treated patients.[1] In high-income countries, treatment paradigms for AML have now shifted to include conventional chemotherapy and/or small molecule drugs directed against biological targets, deemed disease-defining.[1–3] Apart from the acute promyelocytic leukemia variant,[4] however, AML remains incurable for a significant number of patients within different disease subgroups. In addition, the incremental survival gain with small molecule drugs is relatively modest,[2,3,5] and the costs associated with therapy, supportive care, and disease-monitoring remain considerable. In low- and middle-income countries, financial constraints often render therapies, considered "standard-of-care" in higher income countries, prohibitively expensive.[6] Increasingly, the rarity of biological subtypes of AML[1] and the availability of multiple drugs targeting unique disease sub-types[2,5,7,8] are also beginning to present challenges to the design of contemporaneous clinical trials. To optimize clinical benefits and the cost-effectiveness of therapy to patients and healthcare systems, as well as to address key clinical hypotheses, an innovative approach for hypothesis testing and identifying best therapy is, therefore, required.

In recent years, the pharmaceutical industry and regulators have increasingly turned to modeling and simulation to investigate drug–drug interactions,[9] assess the exposure and toxicological impacts of various compounds,[10,11] and reduce reliance on animal experiments for identifying new products.[12] In contrast, physicians have depended solely on the statistical output of adequately powered clinical trials to guide treatment decisions. The existence of clinical trial data and associated publicly available genomic datasets, along with increasingly sophisticated mathematical and computational methodologies, presents a significant opportunity to make progress in the challenging arena of AML therapeutics. Here, we highlight three problem areas relevant to the therapy or monitoring of AML that could benefit from an integrated biological and mathematical approach.

"Plenty"—AML with FLT3 Gene Variants

In AML characterized by the presence of *FLT3* gene variants, a number of FLT3 inhibitors (FLT3i) have been developed.[2,5,7,8] In separate randomized clinical trials, these inhibitors have been shown to confer a small but significant reduction in relapse risk, with survival benefit when administered sequentially with intensive chemotherapy. Despite the abundance of FLT3i on offer, not all patients benefit from their inclusion in treatment pathways, and unanswered questions remain regarding the choice of FLT3i and chemotherapy backbone required to optimize outcomes in individual patients. Logistical challenges will, however, render direct comparisons of different treatments and FLT3i clinical trials infeasible.

"Uncertainty"—Measurable Residual Disease Monitoring

When faced with uncertainty regarding relapse risk in AML, the decision to customize therapeutic interventions based on relapse risk can be guided by molecular genetic or leukemia-associated immunophenotypic measurements of residual

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disease, known as measurable residual disease (MRD), which offers greater sensitivity than conventional laboratory techniques including morphological assessment or routine immunophenotyping.[13] While the prognostic value of MRD detection is well-established for some disease subtypes at predefined time-points following therapy,[14] in others, disease relapse can occur despite an MRD "negative" test result. Recent data also indicate the predictive potential of MRD to inform pre-emptive therapeutic strategies that improve patient outcomes.[15] The prospect of frequent MRD monitoring, however, often requires repeated bone marrow biopsies, and is unappealing to many patients. Additionally, technical and financial considerations pose a barrier to the universal adoption and reliability of MRD measurements in the treatment pipeline. Consequently, a less intrusive, and potentially more reliable, means of informing therapeutic decisions requires consideration.

"Paucity"—AML with *TP53* Gene Variants

In AML characterized by complex karyotypic abnormalities and biallelic dysfunction of the tumor suppressor gene *TP53*, treatment options remain severely limited.[16] The median survival of patients continues to be disappointingly stagnant, despite various attempted genotoxic or nongenotoxic therapeutic approaches, highlighting a substantial unmet need.[17] Traditionally, *TP53* mutations are categorized under missense or nonsense mutational subtypes. Efforts to establish correlative studies between mutation subtype and predicted biological function, clinical phenotype, and functional evolution in response to selective pressures of therapy have been hindered across studies. This is primarily due to restricted patient numbers with a unique genotype, treatment heterogeneity, and limited genomic and functional characterization at diagnosis, response, and relapse. An alternative, strategic, laboratory data-driven approach may be helpful to overcome the absence of biological information on disease evolution in patients and to identify novel treatments.

A Proposal for an Integrated Solution

With the increasing diversity of measurable biological variables, and their subcellular characterization, the opportunities for mechanistic (bottom-up) modeling have expanded significantly in recent decades. In particular, higher-dimensional partial differential equation (HD-PDE) strategies have been successfully employed in predicting resistance phenomena for solid tumors, allowing the simultaneous exploration of correlated dynamics across multiple biochemical variables.[18,19]

In the case of AML, where spatial dynamics are more challenging to measure in clinical practice and are not routinely considered during disease evaluation, *in situ*, there is potential to utilize these additional dimensions of the model to predict "leukemic cell escape" to sanctuary sites that decreases exposure to disease-modifying therapy, or results in false-negative results during MRD testing. Likewise, individual mutations in, for instance, FLT3 or TP53, can be quantitatively explored, in conjunction with multiple, existing therapeutic strategies, with no patient exposure. Downstream effects of these mutations, such as in ligand modification, can also be tracked and modeled to produce an intricate and realistic model of fundamental, intrapatient, tissue-scale dynamics, informing overall disease response. In addition, increased biochemical resolution, through integration of pharmacodynamics of disease modifying therapies with pharmacokinetics, including pharmacogenetics and pharmacogenomics, will allow for quantitative simulation of relative drug and metabolite concentrations within the cell, and a subsequent investigation of clinical and biological implications.

For such models to have a meaningful impact, however, seamless integration into a data-driven modeling pipeline with multiple parallel processes is essential. Once data is collected and systematically separated into "fitting" and "validation" sets, initial HD-PDE modeling can commence. This involves mechanistically quantifying and modeling compound-related cell-scale data, ideally within a pharmacokinetic model super-structure. Subsequently, outcomes from these simulations should be compared with the "fitting" dataset (without "validation" data), in an iterative process that may require modeling updates at every scale. Finally, the finalized HD-PDE model may undergo comparison against the "validation" dataset in a process itself known as "validation," where the model's future predictive capacity is determined based on how well it aligns clinical procedures with outcomes. This iterative process results in a fully parameterized mechanistic model with clinical relevance.

The exciting step would indeed be the utilization of this model to explore new clinical territory, such as the novel comparison of existing treatment options for the same indication, or in heterogeneous patient groups or subgroups, prognostic and predictive risk-stratification for MRD measurements, and therapeutic advances in areas of significant unmet need. It is now prime time for clinical trial-driven attempts, aimed at optimizing necessary treatment, to be complemented with bold, cutting-edge, computational solutions.

Conflict of Interest
None declared.

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