Personalized Therapy for Acute Myeloid Leukemia

Christopher S. Hourigan and Judith E. Karp

Summary: Patient-specific ex vivo drug sensitivity and resistance screening can identify rational drug candidates for the testing of personalized targeted therapy. An iterative approach of genomic and drug susceptibility characterization at sequential time points during clinical trials of targeted therapy in acute myeloid leukemia may be useful both for characterizing mechanisms of resistance and clonal evolution and also for identification of novel therapeutic targets and drug combinations. Cancer Discov; 3(12):1336-8. © 2013 AACR.

See related article by Pemovska et al., p. 1416 (9).

Over the past 5 years, the application of advances in genetic sequencing technology, analysis, and interpretation has revolutionized our understanding of acute myeloid leukemia (AML) biology (1–3). Knowledge of somatic mutations in AML has already demonstrated clinical relevance by improving our ability to determine prognosis using pretreatment risk stratification (4) and/or high-sensitivity measurements of disease burden (5). Unfortunately, this information has had minimal impact therapeutically, with typical intensive AML treatment in both the initial induction and salvage setting remaining the 40-year-old cytotoxic chemotherapy combination of a topoisomerase II inhibitor (e.g., daunorubicin or idarubicin) and cytosine arabinoside, sometimes with the addition of a third agent. This new wealth of genetic data regarding the origins (2) and frequency (3) of common recurrent mutations seen in AML and the clonal heterogeneity at, and differences between, presentation and relapse (1) has, however, opened up the possibility for truly personalized therapy based on direct targeting of aberrant pathways within one individual’s own AML clone(s). Recurrent genetic mutants leading to signaling pathway disruption have previously been identified in a wide variety of solid tumors (and in chronic myeloid leukemia [CML]), and targeted therapies in the form of small-molecule inhibitors and monoclonal antibodies have already been tested and approved for many of these mutated proteins (6). Unlike in the case of CML, however, no single driver mutation is present in all cases of AML (3), and this wide genetic diversity, with many possible cytogenetic and molecular subclassifications, makes the testing of targeted therapy using conventional clinical trial design challenging (7). In addition, in many targeted agents tested, including one recently tested in AML (8), though initial response rates may be impressive, unfortunately, the median duration of response is often modest due to relapse from a drug-resistant malignant cell population. The observation has also repeatedly been made that the presence of the genetic abnormality itself is not always a perfect predictor of initial clinical response to targeted therapy, with responses seen even in those not expressing the proposed “target” and lack of response seen in a significant fraction of those expressing the “target” (8), highlighting the gaps in our understanding of the often broad promiscuity of “targeted therapy” and the difficulty of translating advances in the laboratory into personalized clinical therapy.

In this issue of Cancer Discovery, Pemovska and colleagues (9) report their proof-of-principle attempt to bridge this disconnect in developmental therapeutics between bench and bedside. Using a library of 187 agents, the authors profiled the drug susceptibility of ex vivo AML patient-derived mononuclear cells as compared with healthy-donor bone marrow aspirate mononuclear cells. The drugs tested included conventional chemotherapies, including agents familiar to practicing hematologic oncologists (e.g., daunorubicin, idarubicin, and cytarabine), but also molecularly targeted drugs already tested and approved for non-AML indications (e.g., dasatinib, trametinib, and temsirolimus) and 64 interesting new investigational agents (e.g., foretinib, dactolisib, and MK-2206). The authors were able to identify a number of targeted agents not yet clinically tested in AML that had considerable specificity for ex vivo AML patient samples, showed that clustering of these AML samples by treatment responsiveness resulted in groupings with some shared genetic features, and found that this ex vivo drug screening could in some cases predict targeted agents that would result in clinical responses. Finally, although it had previously been shown by genetic techniques that the predominant clone at AML relapse may differ from the clone at presentation before treatment (1) and that these genetic differences may include changes in the expression of genes associated with response to chemotherapy (10), importantly, this work also demonstrated that the observed changes in clonal heterogeneity at relapse following targeted therapy are associated with changes in both drug

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resistance and drug sensitivity. Repeat molecular profiling and drug susceptibility testing at relapse following targeted therapy allowed hypotheses to be generated regarding the mechanism of action of resistance to that drug and potentially synergistic combinations of targeted therapy to be identified.

The ability to determine sensitivity to therapy in the laboratory before clinical treatment, with analogy to the success of the approach of antibiotic susceptibility testing in microbiologic disease, has long been an aspiration in AML. Although the work by Pemovska and colleagues (9) adds considerably to previous work in this field, several key caveats remain that prevent direct routine clinical application at present. First, the use of viability as the readout in the screen of drug activity does not account for all of the potential mechanisms of action of some of the most interesting new agents (e.g., increased sensitivity to apoptosis or immunomodulation) and does not provide any information on synergies that may result from combinations and particularly permutations of timed and/or sequenced multiagent therapy. Second, screening of nonsorted patient mononuclear cells gives information regarding some of the most cytotoxic drugs for the average of the oligoclonal AML population present at the time of testing but may not give any useful information regarding drug susceptibility of clones present in the minimal residual disease (MRD) and/or leukemia stem cell (LSC) state that will be ultimately responsible for relapse (1, 5, 11).

Finally, the role of the microenvironment in AML is being increasingly recognized, not only for the role that stromal cells play in chemotherapy resistance of AML blasts, but also for the role AML blasts have on normal hematopoietic differentiation, aspects that, along with patient tolerability of novel combinations and the role of the immune system in leukemia control, will not be addressed with this ex vivo screening methodology.

The screening technology described by Pemovska and colleagues (9) does, however, offer a rapid and low-cost “hypothesis-generating” method to identify new classes of drugs with potential utility in AML from the ever-growing catalog of molecularly targeted agents already approved for other indications. Importantly, this screening can be individualized to a particular patient’s own disease at that particular time point, allowing real-time personalization of targeted therapy. Although the clinical responses reported here in the salvage setting were modest and transient, and the diversity of potential testable agents precludes individual testing of all agents alone and in combination in a traditional clinical trial paradigm, the general principle of salvage therapy based on quantitative data from ex vivo sensitivity testing as compared with “physician’s choice” could be tested formally in a randomized clinical trial setting. Perhaps more importantly, by integrating genomic analysis and repeat drug sensitivity and resistance testing on sequential patient samples, the iterative systems approach described in this work provides a method for the analysis of treatment failures following treatment with targeted agents. On the basis of the recognition that pathway dependencies may be clone-specific in an oligoclonal disease such as AML, this approach may identify genotype-phenotype correlations regarding resistance to targeted therapy, novel driver mutations/targets in the relapse samples, and, potentially, combinations of agents that may prevent such clonal relapse. Excitingly, the development of microfluidic and other novel technologies suggests the possibility that in the future one might be able to perform the screens described here on a considerably smaller scale, which would allow more detailed clone-specific determination of drug sensitivity and resistance, perhaps even at a preclinical relapse stage of the MRD/LSC level. Finally, just as genetic information as a surrogate for leukemia disease biology is increasingly integrated into our pathologic diagnostic criteria, the potential exists for the pattern of response to therapy to be a useful tool to help classify the diverse set of diseases we know as AML into meaningful and actionable subcategories. The high-throughput drug susceptibility screening performed in an iterative manner as described here, when combined with deep genomic characterization and high-sensitivity measurements of disease burden/treatment efficacy performed during clinical trials of novel therapies, may represent important correlates as we attempt to move beyond our current “one size fits all” approach to induction and salvage therapy in AML.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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