Venetoclax response prediction in acute myeloid leukemia: are we *Finnish*-ed with uncertainty?

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Venetoclax-based regimens for newly diagnosed patients with acute myeloid leukemia (AML) who are not suitable candidates for intensive induction chemotherapy have had rapid and widespread uptake. There are at least two reasons for this: (i) there was previously no consensus on or enthusiasm for a standard-of-care therapy in this population, and (ii) outcomes from the venetoclax treatment arms were regarded as clinically impactful.[1,2] As we settle in to the post-venetoclax AML era, one thing is clear: those of us who work in the AML field are greedy. We have quickly become accustomed to a well-tolerated therapy with the potential for rapid and deep remissions, and we are done with marveling at response rates in the 60-70% range. Attention has turned to the 30-40% who do not respond to this regimen. We look forward to a future in which we develop interventions to augment or replace venetoclax-based regimens, but to reach this promised land, we must be able to reliably recognize, *a priori*, those patients least likely to respond.

Once upon a time, when intensive induction chemotherapy was the only reasonable intervention for a patient with newly diagnosed AML, rules were written regarding who was and who was not likely to respond to these regimens. After decades of experience using induction chemotherapy, those rules were codified into prognostic systems that judgmentally labeled AML: the hoped-for "favorable" strain, the much-feared "adverse" flavor, and the murky "intermediate" group. Of course, these characteristics were never inherent to AML, but were instead a reflection of response to a particular treatment. In a world with one treatment, however, this subtlety was lost, and these categories came to define the disease subtypes themselves, not describe their response to induction chemotherapy. When another effective treatment arrived, this one with a wholly different mechanism, we had to be reminded that the traditional labels, defined by response to intensive chemotherapy, could not be extrapolated without rigorous study and testing. Indeed, as we have gained experience with venetoclax, we have learned that some traditional risk factors, such as adverse cytogenetic profiles, do not carry adverse implications.[3] Others, such as *TP53* mutations, still do,[3] and still others that had previously been prognostically neutral, such as *IDH* mutations, are associated with better responses.[4] But we cannot limit our analyses to traditional risk factors; biases such as biases such as these, when attempting to uncover predictors for a novel therapy, have the potential to prevent the discovery of new and important factors that may not involve chromosomal abnormalities or gene mutations.

In this issue of *Haematologica*, Kuusanmaki *et al.* and the Finnish group make further progress in advancing the field of venetoclax response prediction in AML.[5] They have been leaders in this movement; 3 years ago, in this Journal, this team made the novel observation that venetoclax response might vary by the degree of maturation of AML, with more primitive disease having higher sensitivity and more mature forms having greater resistance.[6] This unexpected observation of stage of differentiation as a predictive marker has since been validated, by our group and others, in retrospective studies of patients receiving treatment and with further mechanistic work.[7,8]

They have now made the logical next step: seeking to predict, prospectively, whether an individual patient might respond to venetoclax with *ex vivo* testing. The authors designed a pilot study for newly diagnosed or relapsed/refractory AML patients who at baseline had bone marrow or peripheral blood sampled, to which multiple measures of *ex vivo* sensitivity testing were applied using multiple culture conditions and measures of efficacy. All patients (N=39) then received a standard venetoclax+azacitidine regimen, regardless of their sensitivity testing results, which were not communicated to the clinicians treating the patients. Comparison of the predicted *versus* actual response yielded an encouraging positive predictive value of 88%, and the *ex vivo* test was able to predict a cohort with superior overall survival.[5]

The group showed that not accounting for heterogeneity

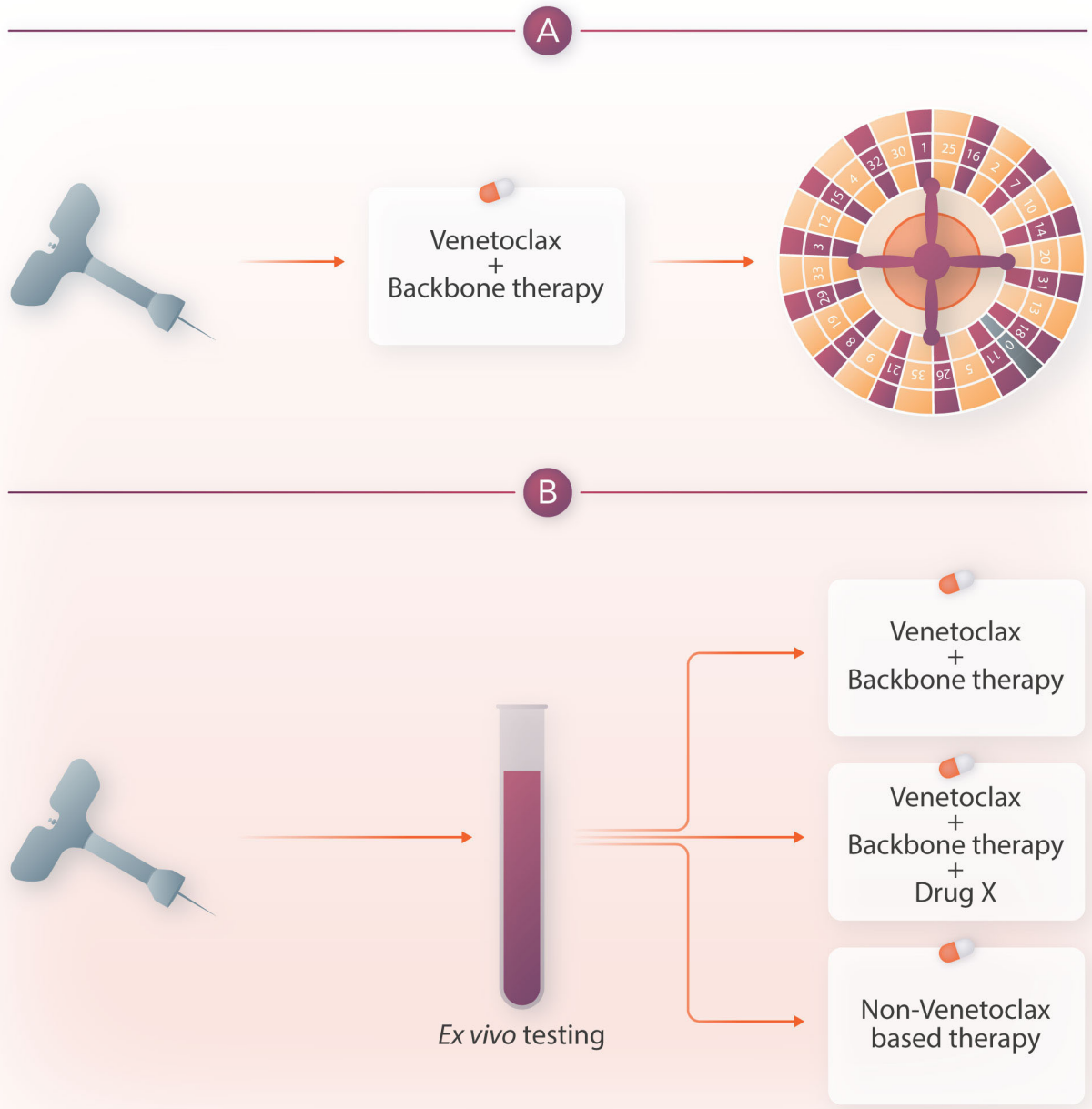

Figure 1. The current and hopeful future of treatment decision-making involving venetoclax in patients with acute myeloid leukemia. (A) Currently, venetoclax-based regimens are prescribed with no insight into the likelihood that the regimen will be effective, akin to a spin of the roulette wheel. (B) In the future, practitioners may have access to rapid and reliable *ex vivo* testing that can help them to recommend a conventional venetoclax-based therapy, a venetoclax "triple combination", or a non-venetoclax-containing regimen.

inherent to this disease led to false predictions of resistance. Interestingly, *ex vivo* efficacy was affected by culture conditions, with the strongest correlations occurring with the use of conditioned media. Furthermore, measurement by flow cytometry had the highest correlation with *in vivo* efficacy.[5] Ultimately, this method largely recapitulates previous preclinical and clinical findings regarding the heterogeneity of response in subsets of cells with some minor exceptions that are likely due to limited representation.

Previous groups have attempted similar measures of predicting drug sensitivity *ex vivo* to guide therapy.[9,10] Importantly, these have largely concentrated on response to conventional chemotherapy agents. Furthermore, accounting for disease heterogeneity, and utilization of multiple media conditions in an iterative fashion, makes the report by Kuusanmaki *et al.* distinctive and particularly exciting.

The authors highlight many of hurdles to developing their assay as a fully-realized clinical test. These include logistical and quality issues around the samples, false predictions, inability to identify small subclones, and scalability issues for its use in multiple laboratories. Addressing these challenges will not be trivial, but this process will be crucial to bringing this type of assay to the clinic.

The manuscript by Kuusanmaki *et al.* is an admirable first step to guiding venetoclax-based therapy prospectively by a response prediction assay that is rapid and accurate. Indeed, the authors report that they are currently using results of this assay to decide whether or not to administer venetoclax+azacitidine to relapsed/refractory AML patients in an ongoing follow-up study. If successful, one can envision a near-future clinical trial design landscape in which patients, after screening, are assigned to venetoclax with a single backbone therapy if they are predicted to respond well, a “triplet” if they might encounter resis-

tance that the third agent could overcome, or a non-venetoclax regimen if they are likely to be refractory (Figure 1). We eagerly anticipate the next phase of their study, and hope we can continue to rely on the Finnish to diminish uncertainty in predicting venetoclax responders in AML patients.

Disclosures

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Contributions

BS and DAP wrote the manuscript.

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