A novel approach to overcome drug resistance in acute myeloid leukemia

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Received: April 13, 2023.
Accepted: May 3, 2023.
Early view: May 11, 2023.

https://doi.org/10.3324/haematol.2023.283099

The prognosis of acute myeloid leukemia (AML) remains poor for the majority of patients suffering from this disease. Undoubtedly, there is a desperate need for new treatments and therapeutic efficacy. In the current issue of *Haematologica*, Assouline *et al.* report on a phase II clinical trial (clinicaltrials.gov: identifier NCT02073838) conducted with vismodegib and ribavirin, with or without decitabine in AML patients.[1] Most of the patients had at least two prior lines of therapy. The authors delve into two aspects of drug resistance, glucuronidation and drug transport into the cells, and help provide future strategies to tackle drug resistance in AML. Drug resistance continues to thwart the treatment success of therapeutics in AML as well as other cancers, leading to poor survival. Overall categories of resistance mechanisms include drug-resistant proteins, genetic alterations, miRNA alterations, and aberrant signaling activation.[2] However, resistance mechanisms and targeting strategies can be specific to certain subtypes and mutations.

A previous study from the same group explored ribavirin as a single agent in M4/M5 AML.[3] In that clinical trial, some clinical responses associated with the reduction of eukaryotic translation initiation factor 4E (eIF4E) levels were seen. Ribavirin competitively inhibits the binding of eIF4E to the m7G RNA cap. The introduction of vismodegib, which targets glioma-associated protein 1 (GLI1) through the Smoothened receptor (Smo), was based on the novel discovery by this group that UDP-glucuronosyltransferase 1 A (UGT1A) and GLI1 have increased expression in resistant AML cells and induce glucuronidation of ribavirin and cytarabine.[4] This glucuronidation is carried out by the UGT enzymes, which leads to inactivation of drug activity, increased water solubility, and elimination of the drug imparted by the conjugation.[5] This group also demonstrated that GLI1-inducible glucuronidation by UGT1A was not limited to these two drugs but included approximately forty other drugs from a variety of families, including nucleosides, antifolates, and anthracyclines.[6] This underscores the importance and potential of targeting UGT enzymes.

In the current study, 23 patients were enrolled, 15 in the vismodegib and ribavirin plus decitabine arm and 8 in the vismodegib and ribavirin arm. Inclusion criteria included elevated eIF4E levels compared to healthy volunteers and functional equilibrative nucleoside transporter 1 (ENT1). The overall response rate was 40% for the arm with decitabine, while there were no responders among the patients who received only vismodegib and ribavirin, although 3 had prolonged stable disease. Of the responders in the vismodegib and ribavirin plus decitabine arm, the majority of them had been previously treated with hypomethylating agents, demonstrating a possible re-sensitization with the vismodegib and ribavirin treatment.

In addition to the exploration of drug resistance through glucuronidation, the authors also evaluated changes in ENT1 levels since many drugs enter cells through ENT1, and reduced levels can lead to resistance. Most patients in this study did have a reduction in ENT1 RNA levels post treatment, indicating a likely acquired mechanism of drug resistance. ENT1 regulation related to drug resistance is not fully understood. Researchers demonstrated that ENT1 removal from the cell surface was induced by bone marrow stroma cell-secreted factors, and this contributed to cytarabine resistance in AML cells.[7] Another recent study found that acquired cytarabine resistance in relapsed AML was related to the downregulation of ENT1 through the inactivation of histone 3 lysine 27 demethylase 6A (KDM6A) which commonly has loss-of-function mutations in cancer.[8] These studies emphasize that ENT1 is related to drug resistance specific to AML. However, although ENT1 has the potential to be used as a resistance predictor, strategies to avoid ENT1-related resistance are lacking and require further exploration.

Since ribavirin is ultimately acting to reduce the oncogenic capacity of eIF4E in a specific way, this raises the possibility of simultaneous targeting of eIF4E by other means to minimize resistance. Targeting MAPK interacting kinases (MNK) in combination with glucuronidation inhibitors may provide such an approach. MNK phosphory-

late eIF4E at serine 209 leading to its activation and promoting its transforming potential, and high nuclear phosphorylated eIF4E have been associated with higher tumor burden in AML patients.[9] Previous studies have shown antineoplastic effects with a breadth of MNK inhibitors on AML cells in *in vitro* and *in vivo* models.[10,11] One of the studies demonstrated that the combination of an MNK inhibitor (SEL201) with 5-azacytidine, a hypomethylating agent similar to decitabine, enhanced the reduction of viability and colony formation.[10] It remains to be seen if specific MNK inhibitors are capable of therapeutic efficacy in patients.

High importance has been placed on understanding mechanisms and progression of resistance in AML. In this work, the authors demonstrated baseline expression differences in these heavily pre-treated patients compared to healthy volunteers, as well as changes over the time of therapy in eIF4E and UGT1A levels. There was a reduction in both UGT1A and eIF4E levels at best molecular response compared to before-treatment measurements, with these increasing again to near baseline at relapse, providing a better understanding of how cells adapt in patients. Other groups have created resistance modeling *in vitro*, such as in a gilteritinib resistance study in *FLT3*-mutated AML where authors examined the metabolic programming in the progression from early to late resistance.[12] They noted that the cells depended on Aurora kinase B (AURKB) in early resistance and suggested using AURKB inhibitors as a strategy to re-sensitize to gilteritinib before the late resistance programming marked by pre-existing *NRAS* mutant subclones ensued.[12] These studies highlight the importance of timing in treatment and the need to further elucidate the mechanisms of progressive resistance.

Overall, the work by Assouline and colleagues provides proof of principle that it is possible to target glucuronidation, and specifically UGT1A levels, in patients without severe toxicity. As noted by the authors, because vismodegib does not target UGT1A levels directly, there are underlying opportunities for the cells to circumvent this pathway inhibition. The development of a more direct inhibitor may lead to more substantial and robust clinical effects. Another study previously found that selective compounds could inhibit UGT1A activity, and researchers are working to optimize these as potential glucuronidation inhibitors.[13] The study by Assouline *et al.* is important and clinically relevant, as it provides a method to overcome one aspect of drug resistance. Using this as a basis, future studies should advance the field further by providing approaches to target glucuronidation, with the ultimate goal being lasting clinical responses.

Disclosures

No conflicts of interest to disclose.

Contributions

CM and LCP wrote the manuscript.

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