Epigenetic gene expression profiling as a predictor of ex-vivo venetoclax sensitivity in acute myeloid leukemia

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INTRODUCTION

Venetoclax-based therapy has transformed AML management, yet response prediction relies predominantly on discrete recurrent mutations (e.g., NPM1, IDH1/2, TP53, FLT3-ITD) and ELN risk, without capturing transcriptional pathway activity that increasingly appears to govern venetoclax sensitivity and resistance.

AIM

We hypothesized that a composite epigenetic gene expression score reflecting functional activity of established AML driver genes would predict ex vivo venetoclax sensitivity independently of mutation status.

METHOD

- We integrated RNA sequencing with ex vivo venetoclax sensitivity data from 239 AML patients at initial diagnosis in the BeatAML dataset (Bottomly et al., Cancer Cell 2022).
- Epigenetic expression score: the unweighted composite of DNMT3A, TET2, IDH1, IDH2, ASXL1, EZH2, and WT1 expression values standardized to a z-score.
- Linear regression models were adjusted for ELN risk, age, and sex.
- Drug specificity was assessed by parallel analysis of azacitidine sensitivity. Bootstrap validation was performed with 1,000 replications.

CONCLUSIONS

Epigenetic gene expression profiling captures ex vivo venetoclax sensitivity independently of and more accurately than NPM1 mutation status alone, with pronounced specificity for venetoclax over azacitidine.

These findings suggest that transcriptional activity of epigenetic regulatory genes may refine prediction of venetoclax benefit in AML beyond current mutation-based and ELN risk classification, warranting prospective validation.

RESULTS

Higher epigenetic expression scores independently predicted lower venetoclax AUC after adjustment for ELN risk, age, and sex (β=−35.9 per SD, p<0.001, adjusted R^2=0.17), indicating greater drug sensitivity. (Figure 1)

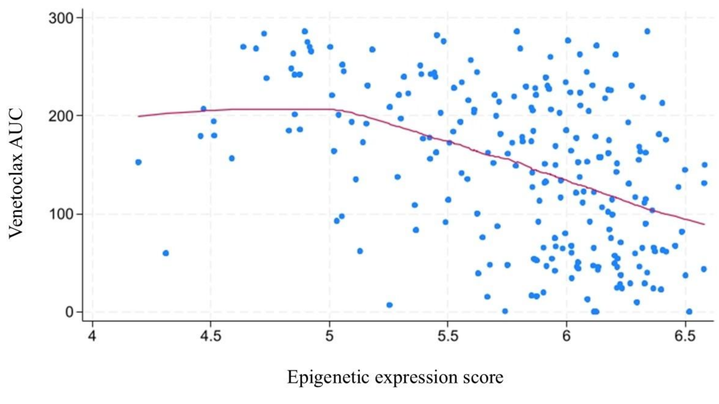

Figure 1: Scatter plot of Scatter plot of ex vivo venetoclax AUC and epigenetic score

- The association remained significant after additionally adjusting for NPM1 and FLT3-ITD mutation status (β=−34.5, p<0.001), neither of which reached significance independently (NPM1 p=0.62; FLT3-ITD p=0.41).
- Patients in the highest epigenetic score tertile demonstrated a mean venetoclax AUC 81 points lower than the lowest tertile as shown in Figure 2.

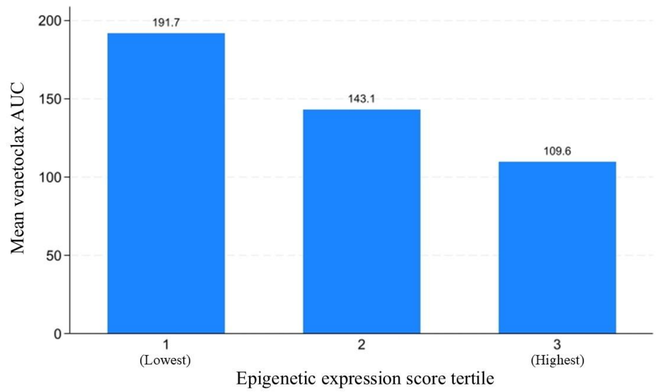

Figure 2: Mean ex vivo venetoclax AUC by epigenetic expression score tertile

- ROC analysis demonstrated an AUC of 0.753 for the epigenetic score compared to 0.542 for NPM1 mutation status alone, with no discriminatory gain from combining both predictors.
- A significant interaction with NPM1 mutation status (p=0.016) identified the strongest association in NPM1-mutated AML (β=−56.7, adjusted R^2=0.46, n=70).
- The epigenetic score predicted venetoclax sensitivity threefold more strongly than azacitidine sensitivity (adjusted R^2=0.17 vs 0.04; drug correlation r=0.19), demonstrating drug specificity.
- Bootstrap validation confirmed robustness of all findings.

CONTACT INFORMATION

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