



High MYC Expression Predicts Poor Survival Outcomes in IDH1/2 mutant AML patients

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BACKGROUND

- *IDH1/2* somatic mutations found at 20% in AML
- Normally, IDH1/2 catalyze isocitrate conversion to alpha-ketoglutarate (α -KG).
- α -KG is an activating co-factor for ten-eleven translocation 2 (TET2), an important epigenetic regulator.
- Mutant IDH1/2 proteins promote α -KG conversion to 2-hydroxyglutarate (2-HG), an onco-metabolite.
- 2-HG inhibits TET2 activity by suppressing 5mC-to-5hmC conversion and thus allowing AML development and maintenance.
- IDH1/2 inhibitors demonstrated promising outcomes in *IDH1/2^{mut}* AML patients.
- Substantial fraction of patients fail to respond to IDH1/2 inhibitors in AML.
- Recent studies have shown MYC prevents the normal myeloid differentiation and cell death by suppressing IDH1/2-TET2 signaling.

OBJECTIVE

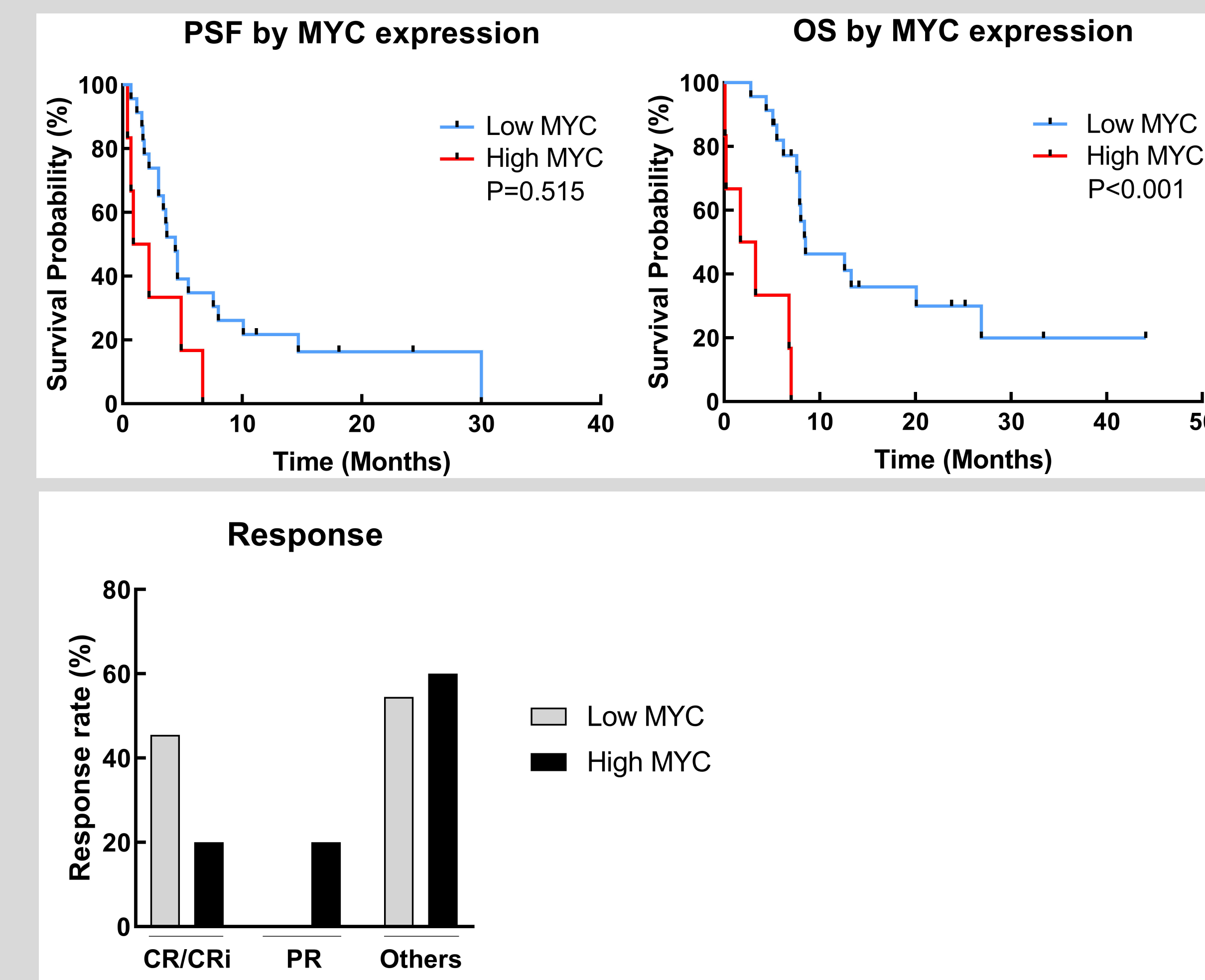
Evaluate if high MYC expression is associated with poor survival outcomes in *IDH1/2^{mut}* AML patients treated with Ivosidenib or Enasidenib.

DESIGN

- Retrospective identification of AML patients with *IDH1/2* somatic mutations based on NGS assessments.
- Clinical and demographic data were recorded.
- Pre-treatment MYC protein levels were assessed by immunohistochemistry (IHC) staining using BM biopsy specimens.
- High MYC expression: $\geq 5\%$ by IHC staining.

RESULTS

- Total of 28 (*IDH1^{mut}*, n=11; *IDH2^{mut}*, n=18; *IDH1/2^{mut}*, n=1) patients
- 12 (42%) patients had secondary AML
- Favorable risk were 9 (32%), Intermediated risk were 11 (39%), Adverse risk were 6 (21%) at AML diagnosis.
- 17 (60.7%) received intensive chemotherapy and 6 (21.4%) hypomethylating agents as 1st-line therapy respectively
- Prior to IDH1/2 inhibitor treatment, 22 (78.5%) and 6 (21.4%) had low and high MYC expression respectively
- Median number of treatments prior to IDH1/2 inhibitors was 3 (1-6)
- Median duration of IDH1/2 inhibitor treatment was 3.2 (0.3-30) months (*IDH1^{mut}*, 3.3 [0.3-30] months; *IDH2^{mut}*, 2.5 [0.7-14.5] months).
- Treatment response was assessed in 27 patients and 11 (40.7%) had CR/CRi (high vs. low MYC, 20 vs. 45.5%, p=.6185).
- The median PFS was shorter in high MYC patients (1.6 vs. 4.4 months, HR=2.348, p=.0515).
- The median OS was also significantly shorter in high MYC patients (2.5 vs. 8.5 months, HR=5.971, p<.0001).



CONCLUSION

In our study, we demonstrated that high MYC expression was associated with significantly shorter PFS and OS in *IDH1/2^{mut}* AML patients. In consistent with our recent studies that showed MYC represses IDH1/2 and TET2 expression in AML, this study suggests that MYC may play an important role in the resistance mechanism of IDH1/2 inhibitors. Additional studies with larger cohorts are warranted to further confirm and validate these findings.