Determinants of Demethylation and Clinical Response In AML Patients Treated With SGI-110, a Novel Subcutaneous (SQ) Hypermethylating Agent (HMA) In a Phase 1 Study

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We analyzed samples from 27 patients with AML. Median age was 64. (range, 29-86). 19 were males (74%). 53% had poor cytogenetics at study entry and 59% had prior exposure to a hypomethylating agent. (Table 1) Overall, peak LINE-1 demethylation generally occurred on Day 8 and correlated strongly with INSL6 demethylation (R=0.81, p<0.0001). In individual patients, peak LINE-1 demethylation ranged from -1% to -39%. (Fig. 1)

We next examined expression of a panel of genes (CD1, P15, P21, DNMT3B, DNMT3A, DNMT1, CTCF) at baseline. High expression of DNMT3B (but not DNMT3A) was associated with a trend for reduced demethylation (R=-0.28, p=0.08). Unsupervised clustering identified the patients into four clusters: A (59%), B (6%), C (11%), and D (24%). Cluster D is characterized by high DNMT1 expression, low P15 expression, low CDA expression, and reduced INSL6 expression (demethylation-average -10% in cluster D compared to -22% in cluster B and C, p=0.01, Fig. 2).

Next, we examined SGI-110-mediated induction of gene expression for 4 genes (P15, P21, DNMT3B and CTCF). (Fig. 3). P15 was the only significantly induced gene (p=0.03), and this was only observed in patients who were treated on the day 5 regimen (compared to weekly x3). In this group of 15 patients with induced P15, peak induction occurred on Day 8 and averaged 2.4 fold. P15 induction was associated with a trend for increased demethylation on Day 8 (R=0.28) and on Day 29 (R=0.37), p=0.05 for both. Of the 27 patients, 5 showed major clinical response (CR). 3 (CRp), 1 (CRi), and 1 (CRi) demethylation averaged -21.1% and -16.9% in responders compared to -11.1% and -11.3% in non-responders. (Table 2). In this group, chemotherapy alone with the 25 mg/m2 dose of SGI-110 resulted in the induction of INSL6 (p=0.01, R=0.425, p=0.027) as well as resistance to SGI-110 (mean 2 score of 10 when non responders compared to 1.75 in responders, p=0.01).

We performed long-term follow-up on all patients. Median follow-up was 5 months (range, 2-13). Of 27 patients, 12 achieved a complete response (CR). 1 was CRp, 2 were CRi, and 9 were CR. The overall response rate was 44%. The median time to disease progression was 3 months (range, 1-12). Resistance to SGI-110 was noted in one patient (110% methylation at Day 29) and one patient (111% methylation at Day 56). 7 patients received two additional cycles of SGI-110 with the same results. In the phase 1 study, 3 patients received a total of 4 cycles of SGI-110 with the same results. In the phase 1 study, 3 patients received a total of 4 cycles of SGI-110 with the same results. In the phase 1 study, 3 patients received a total of 4 cycles of SGI-110 with the same results.

Conclusions

As a therapeutic dose of SGI-110, we identified a gene expression signature (high INSL6, low P15, low CDA) associated with reduced demethylation and resistance to SGI-110 and we find trends for associations between demethylation and response, as well as sustained P15 induction and response. These associations will be further investigated in the ongoing Phase 2 study of SGI-110 in AML.

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References

