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Determinants of hypomethylation and clinical responses in relapsed/refractory AML patients treated with SGI-110, a novel hypomethylating agent in a phase 1/2 study

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Abstract

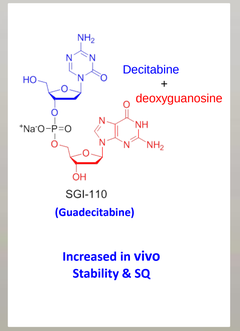
SGI-110 (guadecitabine) is a dinucleotide of decitabine and deoxyguanosine and a novel subcutaneous (SQ) hypomethylating agent. In a previous Phase 1 (dose escalation) study, we found in relapsed/refractory (r/r) AML patients who were treated with SGI-110 (36 mg/m^2-125 mg/m^2) subcutaneously (SQ) daily for 5 days a correlation between low LINE-1 demethylation induction, a three gene expression classifier score (low CDA, low P15 and high DNMT3B) and resistance to SGI-110. Here, we analyzed r/r AML patients (n=122) from Phase 1/2 studies treated at pharmacologically effective doses of SGI-110 looking for determinants of hypomethylation and response. Phase 1 patients with r/r AML (n=27) who were treated at a therapeutic dose range of SGI-110 (36 mg/m^2 - 125 mg/m^2) by SQ daily for 5 days. Phase 2 study r/r AML patients received 60 mg/m^2 SQ daily for 5 days (n=22), 90 mg/m^2 SQ daily for 5 days (n=25) and 60 mg/m^2 SQ daily for 10 days (n=48). Global DNA methylation at pre/post treatment was estimated by bisulfite-pyrosequencing for the LINE-1 repetitive sequence. We also examined expression of a panel of genes (CDA, P15, P21, DNMT3B, DNMT3A, DNMT1, and CTCF) at baseline by quantitative RT-PCR.

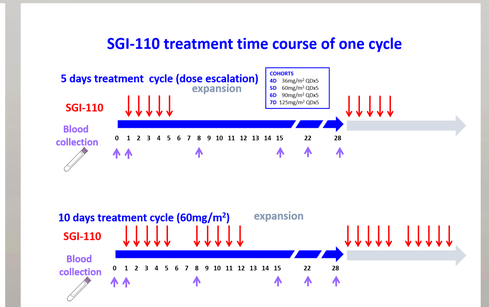
We analyzed samples from 122 patients with r/r AML. Median age was 59.6 (range, 23–86), 75 were males (61.5%). Overall, peak LINE-1 demethylation generally occurred on day 8 after daily x 5 treatment, or on day 8 or 15 after daily x 10 treatment(Fig.1). In individual patients, peak LINE-1 demethylation ranged from +4.9% to -56.3%. In 122 r/r AML patients, 28 showed overall remission (23.0 %, 15 CR and 13 CRi/CRp). Unsupervised clustering by expression of a panel of genes at baseline grouped the patients into two clusters: A (N=95, response rate = 29.5 %) and B (N=27, response rate = 0 %). Cluster B is characterized by high DNMT3b expression, low P15 expression, low CDA expression (average Z-score 1.44 ± 0.26 in cluster B compared to -1.26 ± 0.14 in clusters A, p<0.0001) and reduced demethylation (demethylation average -14.2 ± 1.90 % in cluster B compared to -26.1 ± 1.38 % in clusters A, p<0.0001)(Fig. 2). Peak LINE-1 demethylation was significantly higher in responders than non-responders (average demethylation -32.33 ± 1.91 % in responders compared to -21.25 ± 1.42 % in non-responders, p=0.0001). (Fig.3) A three gene classifier score (low CDA, low P15 and high DNMT3B) was associated with low LINE-1 demethylation (R=0.27, p=0.0034) as well as resistance to SGI-110 (mean Z-score -0.75 in non-responders compared to -1.67 in responders, p=0.014)(Fig.4).

In a phase 1/2 study of SGI-110, we identified in r/r AML patients a gene expression signature (high DNMT3B, low P15, and low CDA) associated with reduced demethylation and resistance to SGI-110 and we found strong trends for associations between demethylation and response.

Background

The majority of patients with acute myeloid leukemia (AML) are elderly and have a poor prognosis despite induction therapy. AML is characterized by frequent DNA methylation changes. Decitabine, a DNA-hypomethylating agent that induces differentiation and apoptosis of leukemic cells, is a well-tolerated alternative to aggressive chemotherapy. But, Decitabine is rapidly eliminated by Cytidine Deaminase, limiting drug exposure time to cancer cells in vivo.
SGI-110 (guadecitabine) is a dinucleotide of decitabine and deoxyguanosine that increases the in vivo exposure of decitabine by protecting it from deamination, and a novel subcutaneous (SQ) hypomethylating agent. In a previous Phase 1 (dose escalation) study, we found in relapsed/refractory (r/r) AML patients who were treated with SGI-110 (36 mg/m^2-125 mg/m^2) subcutaneously (SQ) daily for 5 days a correlation between low LINE-1 demethylation induction, a three gene expression classifier score (low CDA, low P15 and high DNMT3B) and resistance to SGI-110. Here, we analyzed r/r AML patients (n=122) from Phase 1/2 studies treated at pharmacologically effective doses of SGI-110 looking for determinants of hypomethylation and response.





Methods

Phase 1 patients with r/r AML (n=27) who were treated at a therapeutic dose range of SGI-110 (36 mg/m^2 - 125 mg/m^2) by SQ daily for 5 days. Phase 2 study r/r AML patients received 60 mg/m^2 SQ daily for 5 days (n=22), 90 mg/m^2 SQ daily for 5 days (n=25) and 60 mg/m^2 SQ daily for 10 days (n=48). Global DNA methylation at pre/post treatment was estimated by bisulfite-pyrosequencing for the LINE-1 repetitive sequence. We also examined expression of a panel of genes (CDA, P15, P21, DNMT3B, DNMT3A, DNMT1, and CTCF) at baseline by quantitative RT-PCR.

Results

Fig. 1 Average LINE-1 demethylation (± SEM) by SGI-110

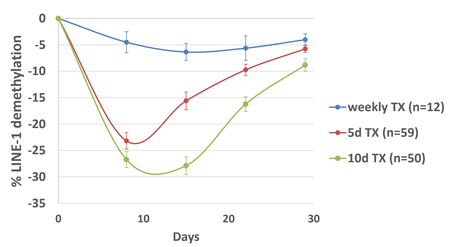


Fig. 3 Peak LINE-1 demethylation was significantly higher in responders than non-responders (average demethylation -32.33 ± 1.91 % in responders compared to -21.25 ± 1.42 % in non-responders, p=0.0001).

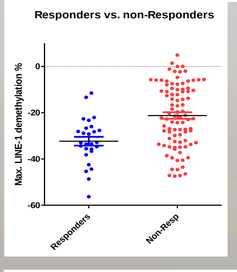


Fig. 4 A three gene classifier score (low CDA, low P15 and high DNMT3B) was associated resistance to SGI-110 (mean Z-score -0.75 in non-responders compared to -1.67 in responders, p=0.014).

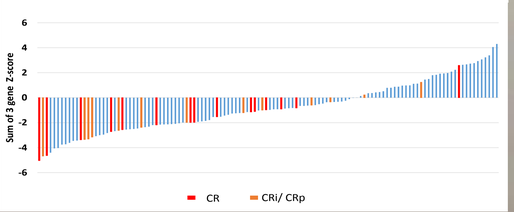
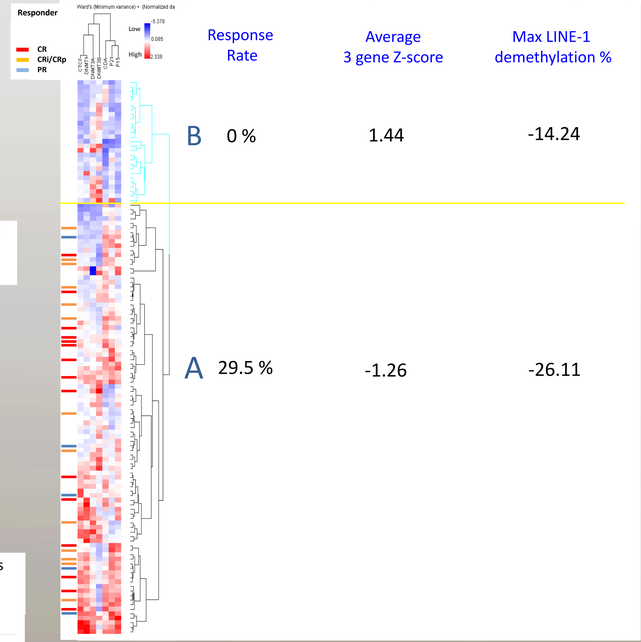


Fig. 2 Unsupervised clustering by expression of a panel of genes at baseline grouped the patients into two clusters: A (N=95, response rate = 29.5 %) and B (N=27, response rate = 0 %). Cluster B is characterized by high DNMT3b expression, low P15 expression, low CDA expression (average Z-score 1.44 ± 0.26 in cluster B compared to -1.26 ± 0.14 in clusters A, p<0.0001) and reduced demethylation (demethylation average -14.2 ± 1.90 % in cluster B compared to -26.1 ± 1.38 % in clusters A, p<0.0001)



	Response Rate	Average 3 gene Z-score	Max LINE-1 demethylation %
B	0 %	1.44	-14.24
A	29.5 %	-1.26	-26.11

Conclusion

In a phase 1/2 study of SGI-110, we identified in r/r AML patients a gene expression signature (high DNMT3B, low P15, and low CDA) associated with reduced demethylation and resistance to SGI-110 and we found strong trends for associations between demethylation and response.