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General AML, FLT3

Prognostic novel markers for OS in AML patients with normal karyotype treated in 7 SWOG trials

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Acute Myeloid Leukemia (AML) is characterized by clinical heterogeneity particularly in patients with normal karyotype (AML-NK) and as such, prognostic markers are required to better stratify the subgroup of patients. In AML, irregular DNA methylation has been shown to occur and epigenetic changes in DNA methylation that correlate with clinical outcomes have been reported. Clinically, there are no epigenetic biomarkers for AML currently used, hence the rationale for this study.

Xiaoyu Qu from the Fred Hutchinson Cancer Research Center, Seattle, Washington, and colleagues recently published their data in Cancer on 21st February 2017. In this study, the authors aimed to identify prognostic methylation biomarkers for Overall Survival (OS) in patients with AML-NK.

212 samples from 202 AML patients treated in 7 SWOG trials were included. Samples were randomly divided into three cohorts; discovery cohort (n = 72, phase 1), model-building cohort (n = 65, phase 2), and validation cohort (n = 65, phase 3). Comprehensive High-throughput Array-based Relative Methylation Analysis combined with Cox proportional Hazards Model (CHARMcox) was applied to the phase 1 cohort to identify Survival-Associated Methylation Regions (SAMRs). SAMRs were then further validated in the phase 2 and 3 cohorts using bisulfite pyrosequencing. An external cohort (n = 93) from The Cancer Genome Atlas (TCGA) AML study (LAML) was used for further validation.

The key results of the study were:

- SAMRs identified at CpG island shores of *LZTS2* and *NR6A1*
- In phase 3, the SAMR at *LZTS2* correlated with OS (P = 0.076); the SAMR at *NR6A1* correlated with OS when FMS-like Tyrosine Kinase 3-Internal Tandem Duplication (*FLT3*-ITD) was taken into account (P = 0.028)
- *LZTS2* and *NR6A1* hypomethlyation was significantly associated with poor OS in patients from the SWOG trials; P = 9.79E-05 and P = 0.0005, respectively
- OS was significantly worse in patients below the median methylation values for *LZTS2* and *NR6A1* in both the SWOG (HR = 1.89; P < 0.001) and LAML cohort (HR = 2.08; P = 0.0057)
- C-statistic in both SWOG and LAML cohort, when *FLT3*-ITD was considered; 0.71
- DNA methylation markers, *LZTS2* and *NR6A1* positively associated with OS in patients with AML-NK and the impact was independent of FLT3-ITD status.

The authors concluded by suggesting that LZTS2 and NR6A1 can readily be used as clinical biomarkers, which can aid in stratifying AML-NK patients for clinical studies. They further suggested that future studies are required to validate the prognostic significance of these markers on other clinical outcomes.

Abstract

BACKGROUND

Aberrant DNA methylation is known to occur in patients with acute myeloid leukemia (AML), whereas methylation signatures and prognostic markers have been proposed. The objective of the current study was to evaluate all CpG sites of the genome and identify prognostic methylation markers for overall survival in patients with AML with normal karyotype (AML-NK).

METHODS

AML-NK samples from 7 SWOG trials were analyzed using a novel genome-wide approach called "CHARMcox" (comprehensive high-throughput array-based relative methylation analysis combined with the Cox proportional hazards model) controlling for known clinical covariates. CHARMcox was applied to a phase 1 discovery cohort (72 patients) to identify survival-associated methylation regions (SAMRs). Subsequently, using bisulfite pyrosequencing, SAMRs were studied in phase 2 model-building (65 patients) and phase 3 validation (65 patients) cohorts. An independent external cohort from The Cancer Genome Atlas (TCGA) AML study (LAML) was used for further validation (93 patients).

RESULTS

Two SAMRs, located at the CpG island shores of leucine zipper tumor suppressor 2 (LZTS2) and nuclear receptor subfamily 6 group a member 1 (NR6A1), respectively, were identified. Multivariable analyses demonstrated that hypomethylation of either LZTS2 or NR6A1 was associated with worse overall survival in the SWOG cohort (P<.001). The prognosis was validated in patients with AML-NK from the TCGA-LAML cohort. Methylation values below the median at both markers predicted worse overall survival (SWOG: hazard ratio, 1.89 [P<.001]; and TCGA-LAML: hazard ratio, 2.08 [P=.006]). The C-statistic was 0.71 for both cohorts, and the impact was independent of the Fms-related tyrosine kinase 3 internal tandem duplication (FLT3-ITD) status.

CONCLUSIONS

The 2 methylation markers, measurable by clinically applicable assays such as bisulfite pyrosequencing, are promising for risk stratification among patients with AML-NK

References

1. Qu X. *et al*. Prognostic methylation markers for overall survival in cytogenetically normal patients with acute myeloid leukemia treated on SWOG trials. Cancer. 2017 Feb 21. DOI: 1002/cncr.30626. [Epub ahead of print].