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P479 DNA METHYLATION PROFILING REFINES THE PROGNOSTIC CLASSIFICATION OF ACUTE MYELOID LEUKEMIA PATIENTS TREATED WITH INTENSIVE CHEMOTHERAPY

Topic: 03. Acute myeloid leukemia - Biology & Translational Research

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Background: Multiple studies have shown that DNA methylation is frequently altered in acute myeloid leukemia (AML).

Aims:

Here we propose a prognostic classifier for the survival of AML patients that describes DNA Methylation-based Risk Assessment ("DMRA"), trained and validated using a total of 538 adult AML patients from two independent cohorts, all treated with intensive cytarabine-based chemotherapy with curative intent, and compared it to the current ELN 2017 classification.

Methods:

Patients from the first cohort were either treated within one of two consecutive clinical trials of the German AMLCG study group or documented within the AMLCG registry. DNA methylation profiles of 377 diagnostic AML samples were generated using Illumina Infinium MethylationEPIC BeadChip arrays, selected based on their chemotherapy regimen (i.e. 7+3, S-HAM, HAM(-HAM), or TAD-HAM). The clinical annotation includes overall survival (OS) and the ELN risk assessment. Our DMRA classifier was trained on the most variable CpG sites genome wide, weighted upon their relevance to OS based on ridge regression. Three prognostic subgroups ("low", "medium" and "high" risk) were identified using cutoffs by optimizing the prediction error to avoid over- and underfitting. We validated our approach by 10-fold cross-validation within AMLCG data, ensuring that samples are either used for training or validation at the same time, as well as using an independent cohort of diagnostic AML samples, selected for cytarabine-based "standard chemotherapy" (n=161, BeatAML).

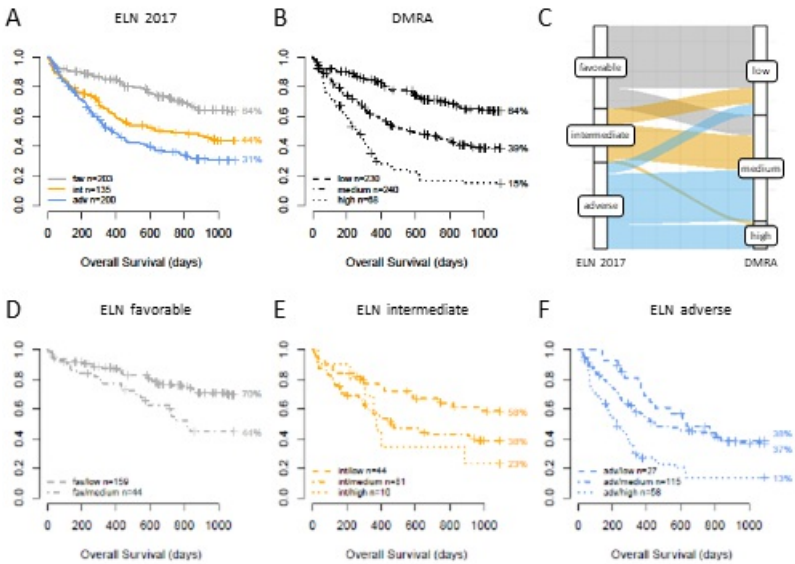
Results:

Overall, the three risk groups defined by DMRA reveal more distinct survival characteristics between each other as compared to between ELN risk groups (Figure 1A,B), with 3-year OS of 64% / 44% / 31% by ELN vs. 64% / 39% / 15% by DMRA. Of note, nearly half of patients were assigned to a different risk group using DMRA as compared to ELN (n=240/538, 45%, Figure 1C).

Importantly, we were able to define more precise risk groups within ELN subgroups, with significant differences in OS. Within ELN favorable AML, 22% of patients (n=44/203) were classified with increased risk (3-year OS 70% vs. 44%, p=0.003 "low" vs. "medium", log-rank test, Figure 1D). Within ELN intermediate AML, 33% of patients

(n=44/135) were classified as low risk AML (3-year OS 58% vs. 38%, p=0.03 “low” vs. “medium”, Figure 1E). Within ELN adverse AML, 71% of patients (n=142/200) were classified with reduced risk (n=27 “low risk”, n=115 “medium risk”, 3-year OS 38% vs. 37% vs. 13%, p=0.0003 “low” vs. “high”, p=0.0002 “medium” vs. “high”, Figure 1F).

Image:



Summary/Conclusion:

Based on this approach, we were able to distinguish clinically relevant prognostic subgroups of AML patients within well described (cyto-) genetic risk groups. Patients with favorable (cyto-) genetics but high-risk epigenetics might benefit from alternative consolidation treatment strategies, such as allogeneic stem cell transplantation. On the other hand, patients with adverse (cyto-) genetics but low-risk epigenetics might be considered for consolidation chemotherapy instead of stem cell transplantation in first complete remission. Finally, patients with both, adverse (cyto-) genetics and high-risk epigenetics, must be considered as very poor risk subgroup with very short OS (median 228 days).

Our results demonstrate that DNA methylation profiling is a feasible and robust approach for risk stratification in AML, able to refine current risk assessment based on (cyto-) genetics alone. We propose that DNA methylation-based risk assessment may serve as a promising complement for current standards in prognostic classification of AML.