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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Comprehensive Molecular Stratification of Patients with AML Treated with CPX-351

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Background: Liposomal cytarabine-daunorubicin (CPX-351) is approved for treatment of acute myeloid leukemia (AML) with myelodysplasia (MDS)-related changes and therapy-related AML. CPX-351 induction has been observed to result in longer periods of bone marrow suppression than with 7+3 therapy. Thus, careful consideration is warranted when selecting patients for whom CPX-351 would provide an optimal risk-to-benefit ratio. It is unknown whether any specific genetic mutations impact outcomes from CPX-351 therapy.
Methods: Forty-one subsequent patients with AML at VCU Massey Comprehensive Cancer Center from 2017 to 2022 were treated with CPX-351 (liposomal cytarabine-daunorubicin). Genetic mutation profiles were obtained from our institutional multi-gene panel next generation sequencing assay. Multivariate analysis was performed using Cox proportional hazards regression. Overall survival (OS) was analyzed via the Kaplan-Meier method. Composite complete response (CCR) was defined as CR + CR with incomplete hematologic recovery + CR with partial hematologic recovery.
Results: The median age of patients treated with CPX-351 was 65.2 years (range, 20.1-78.5). Median ECOG performance status was 1 (range, 0-2) and Charlson Comorbidity Index was 4 (range,2-14). The majority (65.9%) of patients had adverse risk per ELN 2022 criteria, mostly with MDS-related and complex cytogenetics (17.1% favorable risk; 14.6% intermediate risk). Multivariate analysis identified mutated *PTPN11* (*PTPN11* ^{mut})and *IDH2* (*IDH2* ^{mut}) as independent risk factors for decreased OS in patients treated with CPX-351. The hazard ratio (HR) for death of *PTPN11* ^{mut} was 2438 (p = 0.017). The HR for *IDH2* ^{mut} was 124.2 (p = 0.022). Mutated *TP53* was also a risk factor for reduced OS, with HR 3.21, but this was not statistically significant. Mutated *SRSF2* (*SRSF2* ^{mut}) was an independent prognostic factor for improved OS with CPX-351, with a HR of 0.0019 (p = 0.017). *ASXL1, TET2, IDH1* and *FLT3-ITD* mutations were associated with improved OS, but these results did not reach statistical significance. For patients with *SRSF2* ^{mut} treated with CPX-351, median OS was 20.5 months, compared to 8.9 months for those without *SRSF2* ^{mut} (HR 0.49 [95% CI 0.28-0.88], p=0.037). The CCR rate was not significantly different between patients with and without *SRSF2* ^{mut} (p=0.66), and measurable residual disease (MRD) status could not be assessed due to unavailable historical data. Patients with *PTPN11* ^{mut} had a median OS of 11.2 months, whereas those without *PTPN11* ^{mut} had a median OS of 21.6 months, although this comparison was not statistically significant (HR 1.51 [95% CI 0.70-3.26], p=0.207). CCR rates were not significantly different between patients with and without *PTPN11* ^{mut}. The median OS for patients with *IDH2* ^{mut} was 16.4 months, compared to 21.6 months for patients without *IDH2* ^{mut} but this difference was not statistically significant.
Conclusions: Among patients with AML treated with CPX-351, *PTPN11* and *IDH2* mutations were independently associated with inferior overall survival compared to those without these mutations. The *PTPN11* gene is involved in RAS pathway regulation and has also been associated with shorter survival in AML in other studies. Here, mutated *SRSF2* was associated with improved survival after CPX-351 induction. *SRSF2* is an RNA splicing factor gene that is frequently found in AML with antecedent MDS but has previously been associated with adverse outcomes after conventional intensive induction chemotherapy. Interestingly, CCR and MRD negativity rates did not differ for patients with these mutations compared to those without at our institution despite the noted changes in survival. These findings remain speculative and warrant further investigation with a greater number of patients in the era of routine MRD assessment. Moreover, controlling for confounders (such as death due to toxicity rather than disease or relapse), the impact of HCT, and frailty were not accounted for in this retrospective analysis. Future work includes identifying the potential impact of cooperating mutations.

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Figure 1. Overall Survival by SRSF2 Mutation Status

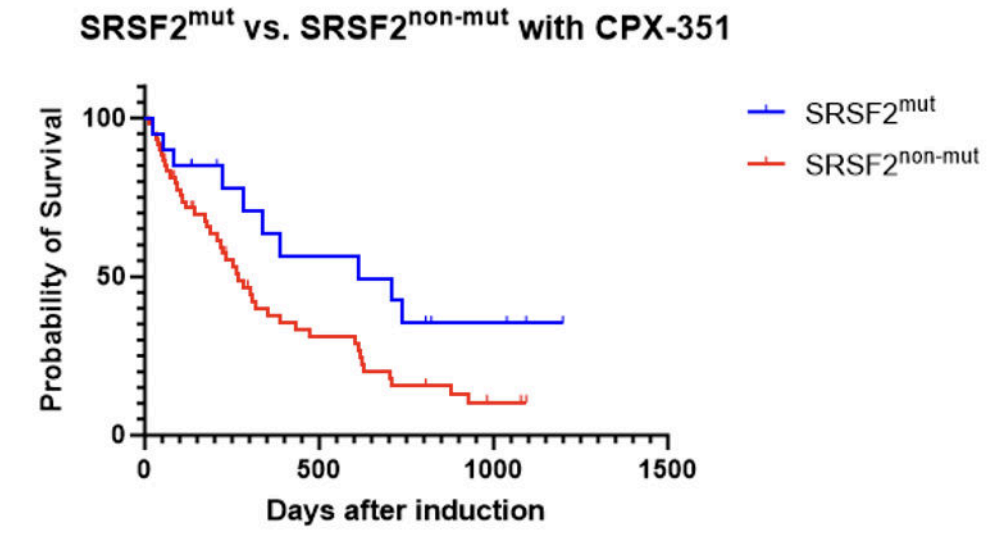

Figure 2. Overall Survival by PTPN11 Mutation Status

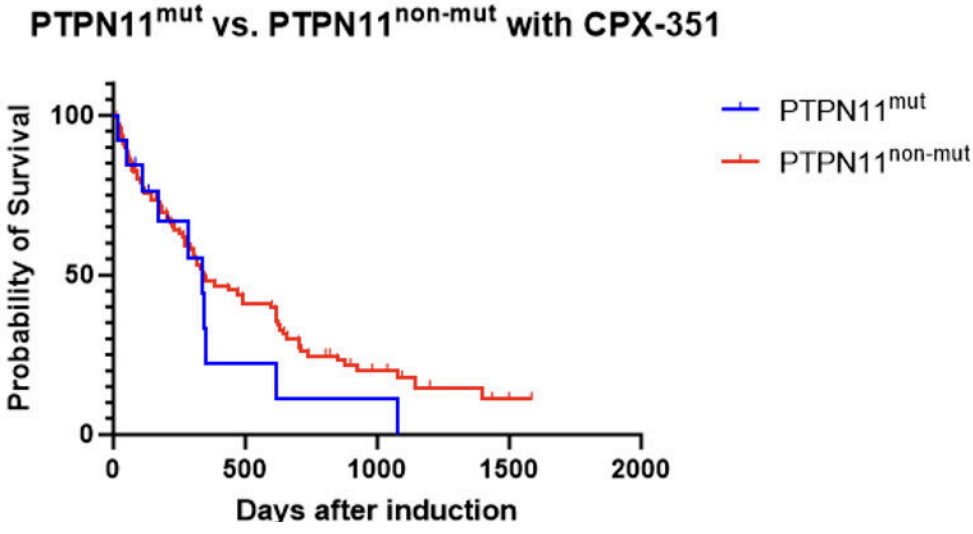

Figure 1

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