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615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

FLT3 Inhibitors in Combination with FLAG-IDA in Relapsed or Refractory Acute Myeloid Leukemia

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1. Introduction

The addition of a FLT3 inhibitor improves overall survival in combination with front-line intensive chemotherapy in acute myeloid leukemia (AML). In the ADMIRAL trial, gilteritinib - a second-generation, type I FLT3 inhibitor - improved survival in relapsed or refractory AML compared to intensive chemotherapy. However, it is unknown whether the combination of a FLT3 inhibitor and intensive chemotherapy improves survival in the relapsed or refractory setting compared with intensive chemotherapy alone or intensive chemotherapy with venetoclax in *FLT3*^{mut} AML.

2. Methods

We analyzed 27 patients with *FLT3*^{mut} AML treated with FLAG-IDA for relapsed or refractory disease from January 1, 2013 to April 18, 2023 at VCU Massey Comprehensive Cancer Center. Baseline disease characteristics were obtained, including molecular profiling either through PCR, NGS, or both, alongside cytogenetic risk, doses of induction regimens, response, and survival. We separated patients that underwent treatment with FLAG-IDA and a FLT3 inhibitor (gilteritinib, midostaurin, or sorafenib), venetoclax, or FLAG-IDA alone. Measurable residual disease (MRD) assays were PCR-based when available; otherwise, MRD was assessed through multiparameter flow cytometry. We used the D'Agostino & Pearson method for normality testing and the Kruskal-Wallis test for between-group comparisons. We applied the Bonferroni correction if multiple comparisons were made. We analyzed survival by the Kaplan-Meier method with significance determined by the log-rank test. The event for calculating the overall survival (OS) was the date of death. Patients were otherwise censored at the date of last contact.

3. **Results**

All 27 patients treated with FLAG-IDA harbored mutations in *FLT3*-ITD (70.3%) or *FLT3*-TKD (29.6%). Twelve (44.4%) patients received FLT3 inhibitors with FLAG-IDA: eight (66.7%) with midostaurin, three (25.0%) with gilteritinib, and one (8.3%) with sorafenib. Five (41.6%) patients received a FLT3 inhibitor (FLT3i) for previously untreated disease, then subsequently received a FLT3i at disease progression. Ten (37.0%) patients received FLAG-IDA without a FLT3i, and five (18.5%) received FLAG-IDA and venetoclax. The median FLT3 variant allele frequency was 33.96% (95% CI, 5.1-63.9) in the FLT3i cohort, 18.0% (95% CI, 8.0-27.0) in the FLAG-IDA cohort, and 5.0% (95% CI, 3.0-29.0) in the venetoclax cohort. The median prior lines of therapy were as follows: three for the FLT3i cohort, two for the FLAG-IDA cohort, and three for the venetoclax cohort ($p = 0.137$).

There was no difference in the achievement of CRc between the FLT3i and FLAG-IDA groups (27.3% vs 33.3%, $p > 0.999$) or between the FLT3i and venetoclax groups (27.3% vs 50.0%, $p = 0.560$). The proportion of responders that achieved MRD negativity was nonsignificantly higher in the FLT3i cohort (75.0% vs 20.0%, $p = 0.206$). The median overall survival nonsignificantly favored the FLT3i cohort compared to the FLAG-IDA cohort (7.7 months vs 4.1 months, $p = 0.992$) and the venetoclax cohort (7.7 months vs 6.3 months, $p = 0.902$).

4. Discussion

The addition of a FLT3 inhibitor resulted in nonsignificantly higher rates of MRD negativity and prolonged overall survival when compared to FLAG-IDA alone or FLAG-IDA and venetoclax. The optimal combination regimen for relapsed or refractory *FLT3*^{mut} AML is unknown, but likely should include a FLT3 inhibitor. The limitations of our study include its retrospective nature;

subsequent FLT3 inhibitor combinations or maintenance strategies may have provided a survival benefit the FLT3i cohort. Therefore, prospective clinical trial designs are needed to further confirm these findings.

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