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

Comparison of Response and Survival with Chemotherapy and Targeted Therapies between IDH ^{mut} Isoforms in Acute Myeloid Leukemia

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1. Introduction

Isocitrate dehydrogenase (IDH) mutations are among the most frequent genetic alterations in acute myeloid leukemia (AML) - they are detected in approximately 20% of patients. While ivosidenib and enasidenib have been approved as targeted therapy for *IDH1* and *IDH2*-mutated AML, respectively, relative outcomes between the *IDH* ^{mut} isoforms remain unclear across various therapeutic options. The aim of this study was to compare response and survival between *IDH*-mutated cohorts of AML when treated with intensive chemotherapy, venetoclax-based strategies, or targeted therapies.

2. Methods

We analyzed 93 patients with newly diagnosed or relapsed or refractory *IDH* ^{mut} AML from January 1, 2013 to April 18, 2023 at VCU Massey Comprehensive Cancer Center. We recorded baseline patient-related and disease characteristics, including dates of regimen initiation and survival. Categorical comparisons used Fischer's exact test. We excluded those with cooperating *IDH1* and *IDH2* mutations. 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

We analyzed 43 patients with *IDH1* ^{mut} or *IDH2* ^{mut} AML treated with first-line intensive chemotherapy with conventional 7+3, CPX-351, or FLAG-IDA with or without venetoclax; we divided the patients into two cohorts: *IDH1* and *IDH2*. We noted no significant differences in the presence of cooperating *NPM1* mutations (25.0% vs 37.0%, $p = 0.529$) or in the proportion of ELN 2022 adverse-risk disease (45.0% vs 40.7%, $p > 0.999$). The composite complete remission (CRc; CR + CRi + CRh) rate for *IDH1* ^{mut} AML was 66.7% (95% CI, 43.7-83.7) compared to 60.0% (95% CI, 40.7-76.6, $p = 0.755$) for *IDH2* ^{mut}. The rate of MRD negativity was 50.0% (95% CI, 18.8-81.2) for *IDH1* ^{mut} and 30.0% for *IDH2* ^{mut} (95% CI, 10.8-60.3, $p = 0.607$). Strikingly, the median overall survival significantly favored the *IDH2* ^{mut} cohort at 25.5 months vs 11.3 months for *IDH1* ^{mut} ($p = 0.047$, Figure A).

Next, we analyzed the outcomes of 19 patients with *IDH* ^{mut} AML treated with first-line venetoclax and a hypomethylating agent (VEN+HMA). We noted a lower proportion of cooperating *NPM1* mutations in the *IDH2* ^{mut} cohort compared with the *IDH1* ^{mut} cohort (36.4% vs 75.0%, $p = 0.170$). Despite this, the CRc rate favored the *IDH2* ^{mut} cohort compared with the *IDH1* ^{mut} cohort (62.5%; 95% CI, 40.7-76.6, vs 20.0%; 95% CI, 30.6-86.3, $p = 0.266$). We noted no significant difference in overall survival between the *IDH1* ^{mut} or *IDH2* ^{mut} cohorts treated with HMA+VEN (12.2 months vs 14.8 months, $p = 0.834$).

In the relapsed or refractory setting, we analyzed 17 patients that received either ivosidenib or enasidenib with or without azacitidine. The CRc for the ivosidenib cohort was 33.3% (95% CI, 5.9-70.0), compared with 28.6% (95% CI, 5.1-64.1, $p > 0.999$) for the enasidenib cohort. The median overall survival favored the ivosidenib cohort at 18.8 months compared to 2.7 months for the enasidenib cohort, which approached statistical significance ($p = 0.069$).

4. Discussion

The median overall survival of *IDH1* ^{mut} AML is significantly worse compared to *IDH2* ^{mut} AML when treated with intensive chemotherapy. The significance of the survival disparity disappears with patients treated with HMA+VEN, suggesting both

isoforms of *IDH* ^{mut} AML benefit from venetoclax. Investigators should be cautious when combining *IDH* ^{mut} AML cohorts while reporting the results of clinical trials in molecularly selected patients.

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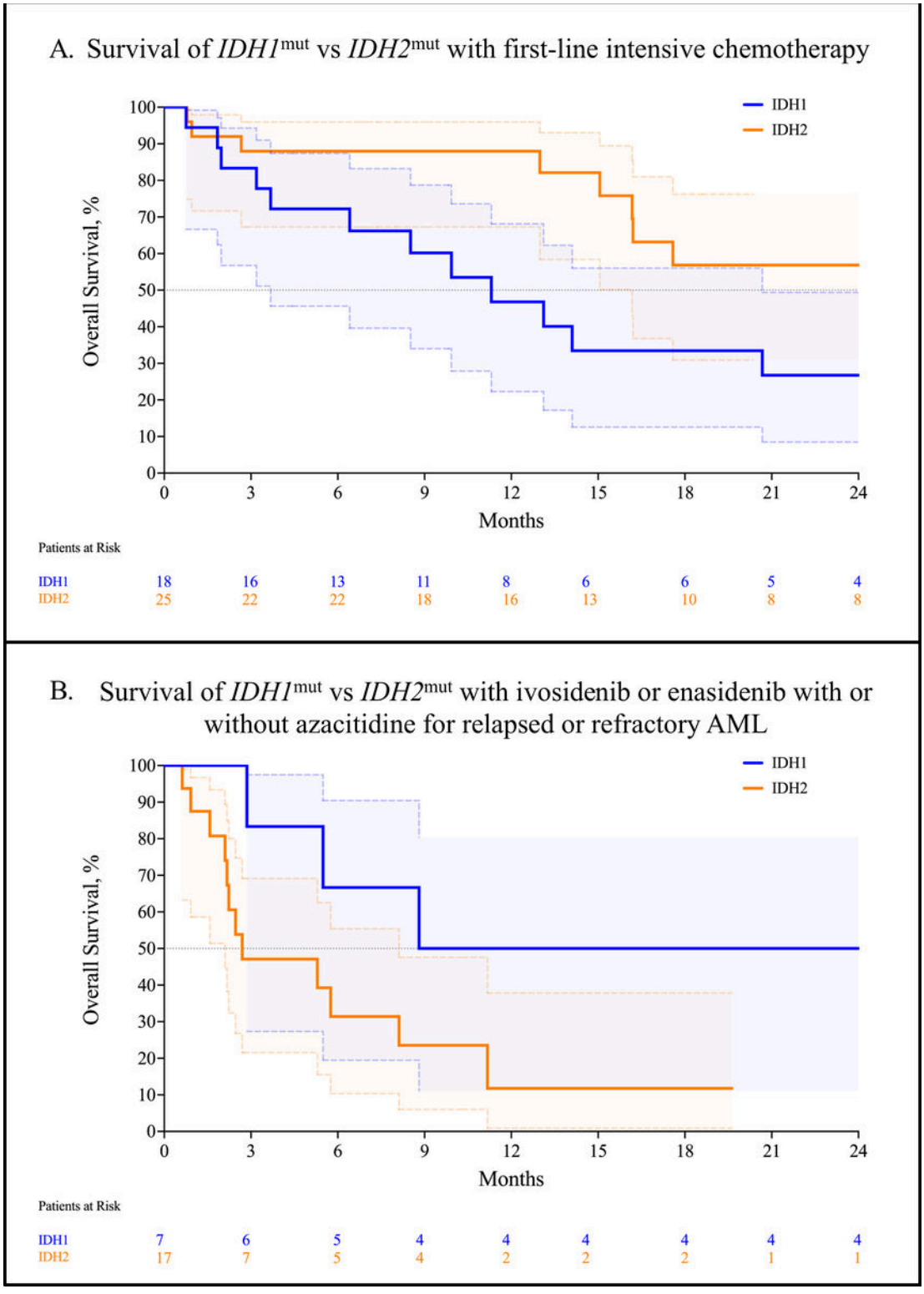

Figure 1

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