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The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Impact of Type of Hypomethylating Agent (HMA) Used on Outcomes of Patients (Pts) with Higher-Risk Myelodysplastic Syndromes/Neoplasms (HR-MDS) - a Large, Multicenter, Retrospective Analysis

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Introduction

HMAs remain the mainstay for frontline treatment of HR-MDS. Azacitidine (AZA) and decitabine (DEC; including oral cedazuri-dine/decitabine) are the only FDA-approved HMAs. However, AZA and DEC have not been compared directly in randomized trials. In this study, we aimed to assess the clinical outcomes of pts with HR-MDS treated with different HMA regimens, focusing on overall survival (OS) and treatment responses.

Methods

The VALIDATE database includes pts with HR-MDS treated with HMA-based therapies in the frontline setting from 14 specialized MDS centers. HR-MDS pts treated with HMA-based therapies in the frontline setting were included. HR-MDS was defined as having an IPSS \geq 1.5 or IPSS-R >3.5 (n=213 pts excluded). Pts were excluded from the survival analysis if age at diagnosis was <18 years (n=1), bone marrow (BM) blasts \geq 20% or unknown at HMA initiation (n=61), or if survival status, follow-up time, date of HMA initiation, or HMA type was unknown (n=28). To be included in the analysis of response based on IWG 2023 criteria (Zeidan A et al, Blood 2023), pts had to have a BM response assessment within 180 days after HMA initiation to allow determination of response (n=290 pts excluded). Time to event analyses were estimated using the Kaplan-Meier method and treatment groups (AZA vs DEC monotherapy) were compared by log-rank test and assessed from the time of HMA initiation. Multivariable Cox regression models were performed among pts treated with AZA and DEC monotherapy to identify predictors of response and OS. This study was supported by an independent research grant from AbbVie.

Results

1,223 pts were screened of whom 919 were included in the survival analysis. Median age was 68 years (Range [R]: 19-95) with 66% males. Our cohort was enriched for pts with adverse genetic features including complex karyotype (38%) and *TP53* mutations (36%). Overall, 76% of pts were treated with HMA monotherapy (56% AZA, 20% DEC) and 24% received HMA-based combination therapy (HMA/VEN: 15%, other HMA combinations: 9%). 38.2% underwent allogeneic hematopoietic cell transplant (allo-HCT). The median HMA duration was 5 cycles (R: 1 - 94).

Due to the small number and the heterogeneity of pts receiving HMA combinations, as well the multiple partner drugs used in these pts (**Table**), we compared OS and responses only between pts treated with AZA (n = 512 pts) or DEC monotherapy (n = 186 pts). In unadjusted analyses, median OS differed by treatment type (p = 0.002) and was 19.8 months (mo) with AZA (95% CI: 17.0 - 23.1 mo) and 14.3 mo with DEC (95% CI: 11.2 - 18.5 mo). Among 629 pts evaluable for response, rates of complete remission (CR) and overall response (ORR) were 14.8% and 48.6% for AZA monotherapy and 5.6% and 50.4% for DEC monotherapy, respectively. In a Cox multivariable regression model (**Figure**) adjusted for age, sex, *TP53* mutation status, complex karyotype, IPSS-M category (compared to very high risk), and receipt of allo-HCT, there was no difference in OS when comparing AZA and DEC monotherapy (Hazard ratio [HR]: 0.95, 95% CI: 0.72 - 1.26; p = 0.740). Variables associated with adverse OS were male sex (HR: 1.52; 95% CI: 1.16 - 2.00; p = 0.002) and presence of *TP53* mutation (HR: 1.50, 95% CI: 1.05 - 2.14; p = 0.027). Conversely, receipt of allo-HCT (HR: 0.26, 95% CI: 0.19 - 0.37; p<0.001) and IPSS-M moderate-high (HR: 0.57, 95% CI: 0.37 - 0.87; p=0.009) and moderate-low (HR: 0.58, 95% CI: 0.36 - 0.95; p = 0.031; both compared to IPSS-M very high risk) were associated with improved OS. Similarly, there were no statistically significant differences in ORR between AZA and DEC (OR: 1.05, 95% CI: 0.66 - 1.68; p = 0.832) in a Cox multivariable regression model adjusted for age, sex, *TP53* mutation, complex karyotype, IPSS-M category, and treatment type.

Conclusions:

Among pts included in the real-world VALIDATE database, there were no significant difference in OS or ORR (IWG 2023) between AZA- and DEC-treated pts in adjusted analyses. Other factors (e.g., *TP53* mutations, complex karyotype) are substantially more relevant to outcomes than the specific HMA used. The small number of pts and heterogeneity of partner drugs in HMA-based combinations precluded robust analyses or conclusions regarding differences in efficacy. Additional analyses evaluating the impact of combinations and molecular subtypes on response and survival will be presented during the meeting as more pts are added to the database.

Disclosures Stahl: *GSK*: Membership on an entity's Board of Directors or advisory committees; *Curis Oncology*: Other: GME activity; *Kymera*: Membership on an entity's Board of Directors or advisory committees; *Boston Consulting*: Consultancy; *Sierra Oncology*: Membership on an entity's Board of Directors or advisory committees; *Haymarket Media*: Other: GME activity; *Rigel*: Membership on an entity's Board of Directors or advisory committees; *Novartis*: Membership on an entity's Board of Directors or advisory committees, Other: GME activity; *Clinical care options*: Other: GME activity; *Dedham group*: Consultancy. **DeZern:** *Appellis*: Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb*: Consultancy, *Caribou*: Membership on an entity's Board of Directors or advisory committees; *Geron*: Membership on an entity's Board of Directors or advisory committees; *Sobi*: Consultancy. **Sekeres:** *BMS*: Consultancy, Membership on an entity's Board of Directors or advisory committees; *Kurome*: Consultancy, Current holder of *stock options* in a privately-held company; *Geron*: Membership on an entity's Board of Directors or advisory committees; *Novartis*: Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis*: Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis*: Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis*: Consultancy, Other: Travel, Accommodations, Expenses, Speakers Bureau; *Stemline Therapeutics*: Consultancy, Speakers Bureau; *Daiichi*: Consultancy, *BMS*:

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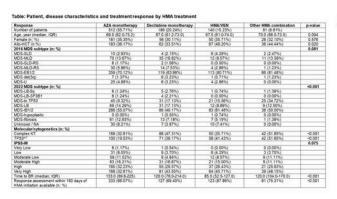
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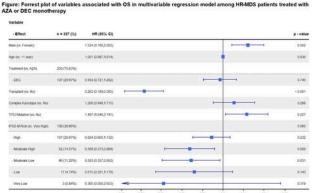


Figure: Forest plot of variable associated with DS immultivariable regression model among HMADS patients treated with AZA or DEC monotherapy. Only patients available for response treated with AZA or DEC monotherapy were included in the Com multivariable regression model earliers are validated in the Com multivariable regression model earliers are real extension and earlier and the control of the Company of t

Figure 1

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