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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Oral Decitabine/Cedazuridine with Venetoclax in High-Risk Myelodysplastic Syndrome or Chronic Myelomonocytic Leukemia: Analysis By Different Response Criteria

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Introduction: Patients with higher-risk myelodysplastic syndromes (HR-MDS) have poor survival. The standard of care for HR-MDS are hypomethylating agents (HMA). The addition of venetoclax (Ven) to HMA has been shown to improve outcomes in acute myeloid leukemia (AML) and potentially in HR-MDS. The combination of oral decitabine/cedazurridine (DEC-C) with Ven has been shown to induce high response rates in patients with HR-MDS. Herein we analyze the responses of patients treated with DEC-C with Ven according to different response criteria. Additionally, we analyze the cytogenetic responses and mutation dynamics.

Methods: We analyzed patients included in a phase I/II single center clinical trial (NCT04655755). diagnosed with treatment-naïve MDS (IPSS intermediate-2 or high) or CMML with excess blasts. Responses were analyzed by the International Working Group (IWG) criteria for MDS of 2006 and 2023, as well as the European LeukemiaNet (ELN) criteria for AML (2022). Cytogenetic responses and mutations were analyzed by conventional cytogenetics/FISH and NGS, respectively.

Results: Between January 2021 and January 2023, 39 patients were enrolled. The median age of the entire cohort was 71 years old (range, 27-94), with 26 (70%) male patients. The WHO 2016 diagnosis was MDS with excess-blasts 1 (n=6, 16%), MDS with excess-blasts 2 (n=24, 65%), CMML-2 (n=6, 16%) and atypical chronic myeloid leukemia (n=1, 3%). The cytogenetic risk according to IPSS was good (n=11, 30%), intermediate (n=12, 32%) and adverse (n=14, 38%). The most common mutations found were *ASXL1* (n=18, 49%), *RUNX1* (n=14, 38%), *SRSF2* (n=11, 30%), *TET2* (n=8, 22) and *TP53* (n=7, 19%).

According to the IWG-2006 classification, the overall response rate was 95%, with 17 (43%) patients achieving complete remission (CR) and 20 (52%) patients achieving marrow CR (mCR). When using the IWG-2023 criteria, the overall response rate was 82%, with 23 (59%) patients achieving CR and 9 (23%) achieving CR with limited count recovery/CR with partial hematologic recovery. Of note, 5 patients achieved mCR according to the IWG-2006 but did not achieved CR by the IWG-2023 due to the peripheral blood count. Moreover, we did not find differences in overall survival (OS) between CR and mCR (OS of 60% for both groups, p=0.5). When using the ELN 2022 criteria for acute myeloid leukemia, the ORR was 80% with 2 patients not responding and 2 patients in a morphologic leukemia-free status (MLFS) (Figure 1).

Both IWG-2006 and 2023 define cytogenetic response as complete disappearance of chromosomal abnormalities present at diagnosis. 14 patients out of 29 (48%) with cytogenetic abnormalities achieved cytogenetic response after a median of 2 courses of treatment (1-9). The IPSS cytogenetic risk of patients responding was good in 1 (7%) patient, intermediate in

8 (57%) patients and poor in 5 (36%) patients, including 3 patients with complex karyotype. Among patients not achieving cytogenetic response, 5 (33%) and 10 (67%) patients had an intermediate and adverse IPSS cytogenetic risk, respectively.
Although molecular responses are not defined in the IWG-2023, we studied the molecular dynamics between diagnosis and best response. 23 patients of the study had molecular data in paired samples at diagnosis and at CR while on treatment. When analyzing the dynamics of each individual mutation, *STAG2* (11/11, 100%), *NRAS* (3/3, 100%), *BCOR* (4/5, 80%) and *IDH1* (2/3, 67%) showed the higher rate of clearance from diagnosis to CR. On the contrary, *ZRSR2* (3/4, 75%), *U2AF1* (3/4, 75%), *TP53* (3/4, 75%), *SRSF2* (5/7, 71%) and *ASXL1* (10/14, 71%) showed the higher rate of persistence from diagnosis to CR (Figure 2). Among all patients in the study, 19 (49%) proceeded to hematopoietic stem cell transplantation (HSCT). Eleven patients had molecular data after HSCT, all achieving complete mutation clearance after HSCT.
Conclusion: DEC-C with Ven achieves a high rate of responses, although with the IWG-2023 criteria responses are lower due to the disappearance of mCR and more strict criteria in terms of peripheral blood count recovery. Almost half of patients with cytogenetic abnormalities can acquire cytogenetic responses, including poor risk cytogenetics. Subclonal mutations (like *STAG2* or *NRAS*) can be cleared with this combination while founding mutations (like *ASXL1* or *TP53*) tend to persist, although HSCT has a potential to eliminate them.

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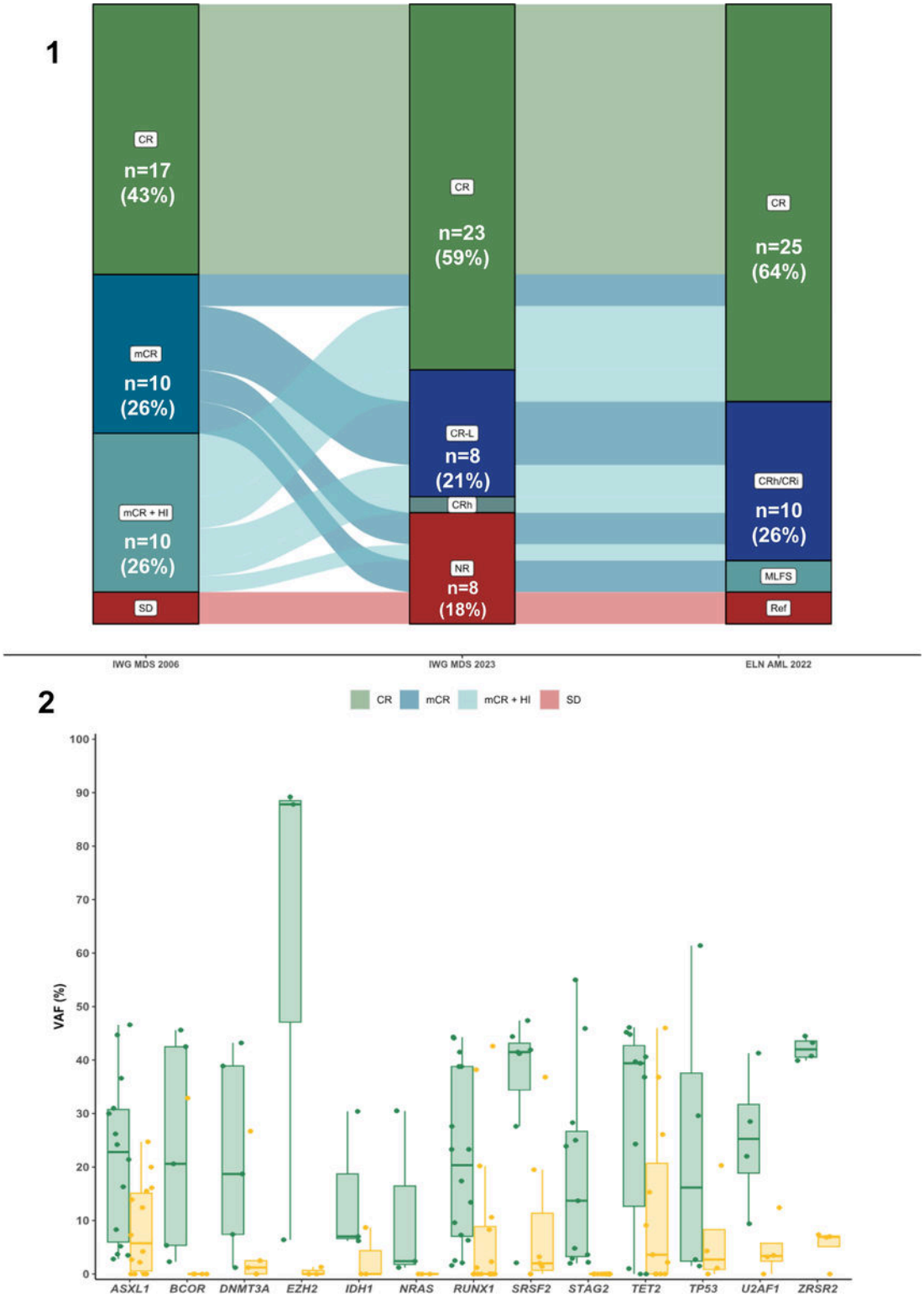

Figure 1

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