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Blood 142 (2023) 6501–6502

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Treatment of Elderly Patients with Higher Risk Myelodysplastic Syndromes with Oral Azacitidine

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Background Oral formulations ofhypomethylating agents decitabine (ASTX727) and azacitidine (cc-486, AZA) were approved respectively for treatment of higher risk myelodysplastic syndromes (HR-MDS) and for maintenance of acute myeloid leukemia after remission. Management of MDS patients with oral agents is relevant to improve quality of life. Oral-AZA has shown activity in lower risk MDS and its use is under evaluation in that setting. There are no data regarding maintenance of response achieved by subcutaneous (sc) AZA in HR-MDS cases by switching to the oral formulation. **Aim** The primary objective of the study was to explore the feasibility of replacing sc-AZA by its oral formulation in patients with HR-MDS in response. Maintenance or improvement of response and, as secondary objectives, patient reported outcome (PRO) and DNA methylation pattern were evaluated. **Methods** A monocentric, pilot phase 2 study was planned to enroll 11 subjects with confirmed diagnosis of MDS, IPSS-R higher risks, aged ≥ 65 years, in CR/CRi, PR or SD with HI after > 6 cycles of sc-AZA therapy (ClinicalTrial.gov NCT04806906). Patients were to receive 300 mg oral-AZA for the first 14-days of each 28-day treatment cycle until absence of benefit or disease progression. Dose of oral-AZA could be de-escalated based on toxicity. At screening and every 4 cycles, IWG response was evaluated. NGS evaluation of somatic mutations and DNA methylation analysis were performed at the same time points. DNA methylation pattern of separated BM CD34 positive cells was determined by Oxford Nanopore. At day1 of every cycle the EQ-5D questionnaire for QoL was administered. Feasibility, safety, tolerability as well as efficacy of oral-AZA were evaluated by monitoring AEs and response/loss of response, time to treatment discontinuation, and PRO. **Results.** As per July 31 st 2023, 11 HR-MDS patients with a median follow up of 167 days (range 47-805) were enrolled in this study. Male/female ratio was 4.5/1 with a median age of 81 yrs (67-88). At diagnosis patients belonged to IPSS-R risk categories intermediate 1/11, high 8/11, very high 2/11; IPSS-M risk categories at start of oral AZA: 3/11 very high, 6/11 high and 2/11 very low. Median number of sc-AZA cycles was 9 (range 7-52), while for oral-AZA median number of cycles was 4 (range 1-10). Oral AZA dose of 300 mg/day was maintained for all patients. DNA methylation was determined with success at baseline and every 4 cycles for all treated patients, and methylation status analyzed. None of the patients had serious adverse events related to study drug. Myelosuppressive effects were transient and Grade1/2. Patients maintained CR (4/11), PR (6/11) and SD with HI (1/11) achieved with sc-AZA, until progression. Therapy was interrupted for progression in 4 patients who evolved to AML after a median of 9 cycles of treatment with oral-AZA. Early discontinuation was experienced in 2/11 patients: in one case following a GI event grade 3 and patient decision to avoid de-escalation of the dose for subsequent cycles, in the second case because of patient reduced compliance. Both patients re-switched from oral to sc-AZA treatment and are still in response (PR). PRO analyses indicated that oral-AZA therapy improved most quality-of-life domains compared to sc-AZA. Treatment is ongoing for 4/11 patients in CR (3/4) and PR (1/4). Responses were observed across all IPSS-M risk categories. **Conclusions** Treatment of HR-MDS elderly patients with oral-AZAis feasible and effective. We observed duration of hematological response with a length consistent with what shown in this patient subgroup, and even after a very prolonged treatment with sc-AZA. Oral AZA was generally well tolerated and AEs did not differ from those observed for sc-AZA.

Disclosures Santini: *BMS, Abbvie, Geron, Gilead, CTI, Otsuka, servier, janssen, Syros:* Membership on an entity's Board of Directors or advisory committees. **Galimberti:** *Abbvie, Janssen, Novartis, Roche, Jazz, Astra Zeneca, Pfizer, Incyte:* Speakers Bureau. **Sanna:** *Janssen:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *Astrazeneca:* Consultancy, Speakers Bureau.

OffLabel Disclosure: cc-486 for HR-MDS patients who obstained at least a stable disease after sc-AZA

https://doi.org/10.1182/blood-2023-190016