ELSEVIER

Blood 142 (2023) 2899–2900

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

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

Antifungal Prophylaxis in Newly Diagnosed Acute Myeloid Leukemia Treated with a Hypomethylating Agent and Venetoclax: A Real-World Experience in Pharmacovigilance

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Background: The oral BCL2 inhibitor venetoclax, in combination with hypomethylating agents (HMA/Ven) improves overall survival in patients with acute myeloid leukemia (AML) either ≥ 75 years or medically unfit for intensive chemotherapy with a tolerable safety profile. It requires significant dose modification when used concomitantly with moderate-strong CYP3A inhibitors, typically azole antifungal agents. In the VIALE-A trial, over 60% of patients in the HMA/Ven arm received antifungal prophylaxis. However, there is no consensus of antifungal prophylaxis in AML patients treated with HMA/Ven given the incidence of invasive fungal infection is overall low and its impact on long-term outcomes remains not well-defined.
Method: In the current study, we retrospectively reviewed the upfront treatment with HMA/Ven in newly diagnosed AML patients who were seen at Moffitt Cancer Center with detailed information of venetoclax dosing and concurrent antifungal use between 2018 and 2021, representing our first three years of real-world experience following accelerated approval of venetoclax by the FDA.
Results: We identified 120 patients who received at least one cycle of HMA/Ven treatment. The median age at diagnosis was 76 years, and 62.5% being male. The baseline disease-related features are shown in Table. A prior history of myeloid malignancy was reported in 42 patients (35%), and 16 of them received HMA based therapy (13.3%). *TP53* mutations were identified in 29 patients (24.8%), and 92 patients (76.7%) were classified as adverse risk based on ELN 2022 risk stratification. In terms of the HMA choice, 79 (65.8%) received azacitidine and rest were given decitabine. The median cycle of HMA/Ven treatment was 4, and HMA dose adjustment was rarely needed in the first 3 cycles (2.0-3.3%). In the first cycle, venetoclax dose was ramped up in 26.9%, and 34.4% received a target dose of 400 mg daily. Its dose required adjustment in about two-thirds of patients during the first three cycles (65.6-72.9%), with the primary reason being concurrent antifungal use (90.2-92.2%). Delays in treatment were found in nearly one fourth of patients (25.5%) during cycle 2 and 3, mainly attributed to poor count recovery and/or bacterial infections. In contrast, invasive fungal infection was uncommon during the first 3 cycles (cycle 1, 3.3%; cycle 2, 2.0%; cycle 3, 3.3%) with a cumulative incidence of 5% (6 patients with 5 possible and 1 proven fungal infections) despite most of them (83.3%) receiving antifungal prophylaxis before the development of invasive fungal infection. Eighty patients (66.7%) achieved complete remission or complete remission with incomplete hematologic recovery (CR/CRi) as the best response. In total, 19 patients (15.8%) ultimately underwent allogeneic stem cell transplant. The median overall survival was 10.8 months, and antifungal prophylaxis during the first three cycles was associated with a consistent trend of inferior overall survival (yes *vs.* no of antifungal use: cycle 1, 8.9 *vs.* 12.5 months, $p = 0.296$; cycle 2, 11.5 *vs.* 15.6 months, $p = 0.206$; cycle 3, 14.1 months *vs.* not reached, $p = 0.063$). In patients who were able to complete ≥ 3 cycles of HMA/Ven treatment, antifungal prophylaxis at any time was still associated with a trend of inferior overall survival (hazard ratio 1.79, 95% confidence interval 0.76-4.20, $p = 0.183$), after adjusting ELN 2022 risk status.
Conclusion: The observed trend of inferior outcomes in newly diagnosed AML patients receiving HMA/Ven with concomitant antifungal prophylaxis might reflect poor count recovery due to underlying disease and/or treatment-related toxicity, which requires further prospective studies.

Disclosures Sallman: *Aprea, Jazz:* Research Funding; *AbbVie, Affimed Gmbh, Gilead, Incyte, Intellisphere, LLC, Molecular Partners AG, PGEN Therapeutics, Inc., Takeda, Zentalis; Advisory board for AvenCell, BlueBird Bio, BMS, Intellia, Jasper Therapeutics, Kite, Magenta Therapeutics, NKARTA, Novartis, Orbita:* Consultancy. **Nelson:** *Stemline:* Consultancy, Speakers Bureau; *sanofi:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *BTG:* Consultancy, Speakers Bureau; *Amgen:* Consultancy, Speakers Bureau; *Seagen:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Padron:** *BMS:* Research Funding; *Incyte:* Research Funding; *Kura:* Research Funding; *Gillead:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Pharmaessentia:* Membership on an entity's Board of Directors or advisory committees; *CTI:* Membership on an entity's Board of Directors or advisory committees. **Komrokji:** *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Rigel, Taiho, DSI:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Geron:* Consultancy; *AbbVie, CTI biopharma, Jazz, Pharma Essentia, Servio:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Lancet:** *MD Anderson:* Consultancy; *MEDTalks:* Consultancy; *The Dedham Group:* Consultancy; *Peer Voice:* Consultancy; *Servier:* Consultancy; *Novartis:* Consultancy; *Jazz:* Consultancy; *Tegus:* Consultancy; *AbbVie Inc.:* Consultancy; *Atheneum:* Consultancy; *BerGenBio / DAVA Oncology:* Consultancy; *Boxer Capital:* Consultancy; *Celgene:* Consultancy, Research Funding; *Globe Life Sciences:* Consultancy; *Jasper Therapeutics:* Consultancy. **Kuykendall:** *Blueprint:* Consultancy, Research Funding, Speakers Bureau; *Protagonist Therapeutics, Inc.:* Consultancy, Research Funding; *GSK:* Consultancy; *Prelude:* Research Funding; *Imago:* Consultancy; *Incyte:* Consultancy; *CTI:* Consultancy; *AbbVie:* Consultancy; *Sierra Oncology:* Research Funding; *BMS:* Consultancy, Research Funding; *Morphosys:* Consultancy, Research Funding; *Novartis:* Consultancy.

Table. Patient and disease characteristics.

Variables (median, IQR; N, %)	N = 120
Demographics	
Age at diagnosis (years)	76 (70-79)
Age >= 75 years	67 (55.8)
Male (%)	75 (62.5)
Baseline disease features	
White blood cell count ($\times 10^3$/uL)	3.3 (1.6-16.2) (n = 95)
Absolute neutrophil count ($\times 10^3$/uL)	0.8 (0.3-2.4) (n = 80)
Peripheral blood blast percentage	17 (1-42) (n = 68)
Bone marrow blast percentage	41 (24-69) (n = 116)
Adverse cytogenetics	45 (39.8) (n = 113)
Somatic mutations	N = 117
NPM1	11 (9.4)
FLT3-ITD/TKD	12 (10.3)
TP53	29 (24.8)
IDH1/2	23 (20.4)
MDS-related genes (ELN 2022 definition)	67 (57.3)
Numbers of somatic mutations	2 (1-3)
Prior history of myeloid malignancy	42 (35.0)
Prior history of HMA exposure	16 (13.3)
ELN 2022 risk stratifications	
Favorable/intermediate/adverse	9 (7.5)/19 (15.8)/92 (76.7)
Treatment	
Azacitidine + venetoclax	79 (65.8)
Decitabine + venetoclax	41 (34.2)
Allogeneic stem cell transplant	19 (15.8)

Figure 1

https://doi.org/10.1182/blood-2023-187206