LETTERS TO THE EDITOR
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Antifungal Prophylaxis in Hypomethylating Agents Venetoclax Combination in AML-Turkish Society of Hematology Subcommittee on Infections and Supportive Therapies in Hematology Survey Study

AML'de Hipometilleyici Ajan Venetoklaks Kombinasyonunda Antifungal Profilaksi-Türk Hematoloji Derneği Hematolojide Enfeksiyonlar ve Destek Tedaviler Alt Komitesi Anket Çalışması

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To the Editor,

Treatment options for acute myeloid leukemia (AML) are improving worldwide, with better remission and survival rates, but also with some side effects. Today, venetoclax, a small molecule inhibitor of bcl-2, in combination with hypomethylating agents (HMAs), is the standard of care for the treatment of AML in elderly patients who are ineligible for intensive chemotherapy. Although this combination therapy, called non-intensive therapy, might initially seem harmless, in clinical practice it carries a significant risk of infection due to prolonged neutropenia with severe cytopenias. However, despite guidelines and expert opinions recommending prophylaxis, the incidence of invasive fungal infections (IFIs) and the need for antifungal prophylaxis (AFP) remain controversial, particularly because of the impact of AFP on disease remission, survival, and drug-related toxicity (1-6). Therefore, as TSH subcommittee on infections and supportive therapies in hematology, we aimed to present the attitude in Türkiye on this subject via a survey study.

The 17-question survey was completed anonymously online by 81 adult hematology specialists. The median age of participants was 42 years and 52.5% were male. 43.2% of the participants work in a Teaching and Research Hospital. Approximately half of the participants have been working in hematology for <5 years. In newly diagnosed/relapsed/refractory AML patients, the most common HMA preference in venetoclax combination was azacitidine with a rate of 92.6%. After ramp-up in the first cycle, 59.3% of participants preferred 400 mg dose of venetoclax and 69.1% preferred 28 days of use. After disease remission, 56.8% of participants used venetoclax 400mg and 25.9% used venetoclax 28 days. Frequent febrile neutropenia, cytopenias, and drug interactions are the most common reasons for changes in venetoclax dose and/or duration. AFP, mostly based on guideline/expert recommendations, was preferred by 76.54% of participants. The most common preferred antifungal agent was posaconazole (69.4%), and approximately 60% of participants used AFP for >3 cycles. Venetoclax with AFP has been widely used at 100mg and >14 days. 86% of posaconazole users preferred venetoclax 70mg or 100mg, while 75% of voriconazole users preferred venetoclax 100mg or 200mg. The survey and the results are detailed in Table 1. There is no statistically significant difference between antifungal use and duration of specialization or institution of employment.

In studies, posaconazole or fluconazole is commonly used as the AFP agent for the first two courses. The primary reason for AFP use is the duration and severity of neutropenia and febrile neutropenia (1,2,7). This

survey study showed that a small proportion of participants in Turkey did not prefer AFP, while there was variability in venetoclax dose preferences when using AFP. Online administration and the level of reliability is the main limitation of the survey. In conclusion, the subcommittee plans to conduct a prospective study to determine the incidence of IFI, toxicities, remission and mortality rates in centers with and without AFP to clinically evaluate the results.

Ethics: The ethical approvel was obtained from the Institutional Ethical Committee of Trakya University (TUTF-GOBAEK 2024/49)
Authorship Contributions: Concept: T.A.K.; Design: T.A.K., V.O.; Data collection and Processing: T.A.K.; Analysis or Interpretation: T.A.K.; Literature Search: T.A.K., V.O.; Writing: T.A.K., V.O.
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Abbreviations:
AML: Acute myeloid leukemia
HMAs: Hypomethylating agents
AFP: Antifungal prophylaxis
IFIs: Invasive fungal infections
TSH: Turkish Society of Hematology

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Table 1. Survey of antifungal prophylaxis in HMA-venetoclax combination in acute myeloid leukemia

Questions	**Responses**
What is your age?	Median: 42 years (32-69) (80 responses)
What is your gender?	Female: 47.5% Male: 52.5% (80 responses)
What is the institution you work for?	Medical Faculty Hospital: 35.8% Training and Research Hospital: 43.2% State Hospital: 7.4% Private Hospital: 13.6%
What is the duration of your expertise?	<5 years: 44.4% 5-10 years: 23.5% >10 years: 32.1%
In Newly Diagnosed / Relapsed/ Refractory AML	
What is your most commonly preferred HMA to use with venetoclax?	Azacitidine: 92.6% Decitabine: 7.4%
What is your most commonly preferred dose of venetoclax with HMAs for the first cycle after ramp-up?	70 mg: 1.2% 100 mg: 21% 200 mg: 14.8% 300 mg: 3.7% 400 mg: 59.3%
What is your most commonly preferred duration of venetoclax with HMAs in the first cycle?	7-10 days: 2.5% 14 days: 11.1% 21 days: 17.3% 28 days: 69.1%
What is your most commonly preferred dose of venetoclax with HMAs after achieving remission?	70 mg: 2.5% 100 mg: 22.2% 200 mg: 17.3 % 300 mg: 1.2% 400 mg: 56.8%
What is your most commonly preferred duration of venetoclax with HMAs after achieving remission?	7-10 days: 8.6% 14 days: 40.7% 21 days: 24.7% 28 days: 25.9%
What are the indications of venetoclax dose reduction?	Cytopenias: 59.3% (48 responses) Drug interactions: 74.1% (60 responses) Frequent FN episodes: 61.7% (50 responses) No dose reduction: 6.2% (5 responses)
What are the indications for reduction of venetoclax duration?	Cytopenias: 75.3% (61 responses) Drug interactions: 22.2% (18 responses) Frequent FN episodes: 80.2% (65 responses) No dose reduction: 12.3% (10 responses)
Do you commonly prefer antifungal prohylaxis in the combination of HMA-venetoclax therapy?	76.54 %
If you prefer antifungal prophylaxis;	
What is your most commonly preferred antifungal agent for prophylaxis?	Fluconazole: 21% Posaconazole: 69.4% Voriconazole: 6.5% Micafungin: 3.2% Caspofungin: 0%
What is your indication to prefer antifungal prophylaxis?	IFI history: 3.22% Guideline/expert recommendations: 43.5% Prolonged neutropenia: 30.6% High risk of febrile neutropenia: 11.3% Physical conditions of the center and high IFI frequency: 12.9%
What is your most commonly preferred duration of antifungal prophylaxis?	First cycle: 21% First 2 cycles: 12.9% ≥3 cycles: 59.7% Other: 6.2%

What is your most commonly preferred dose of venetoclax with antifungal prophylaxis?	70 mg: 3.2% 100 mg: 61.3% 200 mg: 22.6% 300 mg: 1.6% 400 mg: 11.3%
What is your most commonly preferred duration of venetoclax with antifungal prophylaxis?	7 days: 8.1% 14 days: 24.2% >14 days: 64.5% Unknown: 3.2%

HMA: Hypomethylating agent, IFI: Invasive fungal infection