LETTER TO THE EDITOR

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Antifungal Prophylaxis in the Treatment Combination of Hypomethylating Agents and Venetoclax for AML: A Survey Study of the Turkish Society of Hematology Subcommittee on Infections and Supportive Therapies in Hematology

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, is the standard of care for the treatment of AML in combination with hypomethylating agents (HMAs) in elderly patients who are ineligible for intensive chemotherapy. Although this combination therapy, referred to as non-intensive therapy, might initially seem harmless, in clinical practice it carries a significant risk of infection due to prolonged neutropenia with severe cytopenia. 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 [1,2,3,4,5,6]. Therefore, on behalf of the Turkish Society of Hematology 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 the participants was 42 years, 52.5% were male, and 43.2% were working in a teaching and research hospital. Approximately half of the participants had been working in hematology for <5 years. In patients with newly diagnosed/relapsed/refractory AML, the most common HMA preference in combination with venetoclax was found to be azacitidine at a rate of 92.6%. After ramp-up in the first cycle, 59.3% of participants preferred a venetoclax dose of 400 mg and 69.1% preferred 28 days of use. After disease remission, 56.8% of participants used venetoclax at 400 mg and 25.9% used venetoclax for 28 days. Frequent febrile neutropenia, cytopenia, and drug interactions were the most common reasons for changes in the venetoclax dose and/or duration. AFP, mostly based on guideline/expert recommendations, was preferred by 76.54% of participants. The most commonly preferred antifungal agent was posaconazole (69.4%), and approximately 60% of participants used AFP for >3 cycles. Venetoclax with AFP is widely used at 100 mg and >14 days, while 86% of respondents utilizing posaconazole preferred venetoclax at 70 mg or 100 mg and 75% of those utilizing voriconazole preferred venetoclax at 100 mg or 200 mg. The survey and the results are detailed in Table 1. There was no statistically significant difference between antifungal use and the duration of specialization or institution of employment.

In previous studies, it has been reported that posaconazole or fluconazole is commonly used as the AFP agent for the first two courses, and the primary reason for AFP use is the duration and severity of neutropenia and febrile neutropenia [1,2,7]. The present survey study showed that a small proportion of participants in Türkiye did not administer AFP, and there was variability in venetoclax dose preferences when administering AFP. The online nature of the survey and the level of reliability of studies based on self-report constitute the main limitations of this research. In conclusion, the Subcommittee now plans to conduct a prospective study to determine the incidence of IFIs, toxicities, remission, and mortality rates in centers with and without AFP to clinically evaluate the results of such treatment.

Table 1. Survey on antifungal prophylaxis in treatment with HMA-venetoclax combination in acute myeloid leukemia.

Questions	Responses
What is your age?	Median: 42 years (range: 32-69) (80 responses)
What is your gender?	Female: 47.5%; male: 52.5% (80 responses)
What institution do 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 cases of 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?	Cytopenia: 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?	Cytopenia: 75.3% (61 responses) Drug interactions: 22.2% (18 responses) Frequent FN episodes: 80.2% (65 responses) No duration reduction: 12.3% (10 responses)
Do you commonly administer antifungal prophylaxis during combination HMA-venetoclax therapy?	Yes: 76.54%
If you administer 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 the indication leading you to administer antifungal prophylaxis?	IFI history: 3.22% Guideline/expert recommendations: 43.5% Prolonged neutropenia: 30.6% High risk of FN: 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%

Table 1. Continued.

Questions	Responses
If you administer antifungal prophylaxis	
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% Unsure: 3.2%

HMA: Hypomethylating agent; AML: acute myeloid leukemia; FN: febrile neutropenia; IFI: invasive fungal infection.

Keywords: Acute myeloid leukemia, Venetoclax, Fungal prophylaxis, Survey

Anahtar Sözcükler: Akut myeloid lösemi, Venetoklaks, Fungal profilaksi, Anket

Footnotes

Authorship Contributions

Concept: T.A.K.; Design: T.A.K., V.Ö.; Data collection and Processing: T.A.K.; Analysis or Interpretation: T.A.K.; Literature Search: T.A.K., V.Ö.; Writing: T.A.K., V.Ö.

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