Which prophylaxis for unfit AML patient?

BHS

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Viale-A study

Table 2. Adverse Events.*

Event	Azacitidine–Venetoclax Group (N = 283)		Azacitidine–Placebo Group (N = 144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious adverse events§	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

DiNardo et al. NEJM. 2020

Viale-A study – prophylaxis recommandation

Anti-infective prophylaxis should be implemented per regional guidelines or institutional standards including appropriate prophylaxis for bacterial, viral and fungal infections. Potential for drug-drug interactions should be considered. Please refer to Table 1 and Appendix G for a description of excluded and cautionary medications.

Anti-infective prophylaxis for bacterial, viral and fungal infections are required for all subjects with ANC of < 500/µL. Institutional infectious organisms and their drug resistance patterns should primarily be considered and the choice of these agents should be based on regional guidelines or institutional standards. Potential for drug-drug interactions should be considered. Please refer to Table 1, Table 2 and Appendix H for list of excluded and cautionary medications and implement dose reductions for venetoclax/placebo as necessary.

VIALE-A study - supplement

Table S5. Antibiotic and Antiinfection Prophylaxis

Generic name	Azacitidine and venetoclax (N=286) n (%)	Azacitidine and placebo (N=145) n (%)
Prophylactic medication in approximately 5% of patients	**236 (83)**	**117 (81)**
Aciclovir	79 (28)	37 (26)
Amphotericin b	14 (5)	7 (5)
Augmentin	23 (8)	9 (6)
Bactrim	57 (20)	20 (14)
Caspofungin	16 (6)	6 (4)
Cefepime	24 (8)	10 (7)
Ciprofloxacin	43 (15)	20 (14)
Fluconazole	44 (15)	26 (18)
Levofloxacin	85 (30)	47 (32)
Meropenem	30 (11)	11 (8)
Micafungin	27 (9)	8 (6)
Pip/Tazo	35 (12)	19 (13)
Posaconazole	43 (15)	21 (15)
Valaciclovir	34 (12)	15 (10)
Voriconazole	17 (6)	8 (6)

DiNardo et al.
NEJM. 2020

EBM – viral prophylaxis

No reported data concerning HSV and/or VZV reactivation in the setting of VenAZA

Primair HSV prophylaxis could be not usefull because (1,2,3)

- Not depleted of CD8 T cells
- Either no demonstration of toxicity again CD8 T cells
- => but recommended in VIALE-A (4) and NHS guideline (5)

No reported data concerning hepatitis B reactivation

- - Still recommended to start prophylaxis for anti-HBC + patients (3)

Vaccination against influenza is recommended (3).

1. Wade J. *Hematology Am Soc Hematol Educ Program* (2006)
2. Jonas et al, leukemia. 2019
3. Sandherr et al. Ann Hematol. 2015
4. DiNardo et al. NEJM. 2020
5. https://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-84-azacitidine-and-venetoclax-covid-19.pdf

CD: cluster of differenciation; EBM: Evidence-based medicine; HBC: hepatitis B core antigen; HSV: Herpes Simplex Virus; NHS: National Health Service; VenAza: Venetoclax and Azacitidine; VZV: Vesicular stomatitis virus

What I Do?

- If there is history of herpetic reactivation and/or patient already under HSV prophylaxis, I deliver acyclovir otherwise, I don’t.

- If there is sign of ancient HBV, I prefer to start primary prophylaxis even there is no rational to do it.

HBV: hepatitis B Virus; HSV: Herpes Simplex Virus

EBM – antimicrobial prophylaxis

- Fit AML patient : depend of local policy (i.e. HOVON) and guideline due to emergence of Resistant bacteria, so more and more we do not delivered it anymore.

Antimicrobial prophylaxis:

Recommendation 1.1 Risk of febrile neutropenia should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer- and treatment-related factors (see Table 1). (Type of recommendation: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2 Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for febrile neutropenia or profound, protracted neutropenia (eg, most patients with acute myeloid leukemia/myelodysplastic syndromes [AML/MDS] or hematopoietic stem cell transplantation [HSCT] treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. (Type of recommendation: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).

Taplitz R et al. JCO.2018

=> Gafter-Gvili A et al. Cochrane Database Syst Rev. 2012

AML: Acute myeloid leukemia; EBM: Evidence-based medicine

EBM – antimicrobial prophylaxis

- Unfit AML patient (+ for ECIL, - for NICE/NHS)

Risk of infection associated with venetoclax:

- No specific impact on immune defense apart from neutropenia.

Recommended diagnostic procedures:

- Standard of care in AML and neutropenic fever and/or infections (A-IIr).

Treatment recommendations:

- Standard of care in neutropenic fever and/or infections (A-IIr).

Recommendations for prophylaxis:

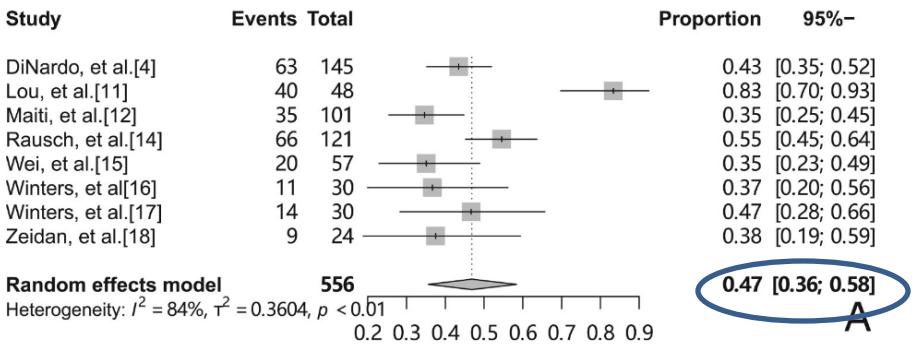
- Standard of care as for AML treatment with intensive chemotherapy (A-IIr).

Further recommendations for prophylaxis:

- Consider antibacterial and antifungal prophylaxis when hypomethylating agents are combined with venetoclax (A-IIr).

Maschmeyer G et al. (ECIL) leukemia. 2022

RATE of neutropenic fever



GUO Y et al. Hematology. 2020

AML: acute myeloid leukemia; EBM: Evidence-based medicine; ECIL: European Conference on Infections in Leukemia; NICE: national institute for clinical excellence; NHE: national health service.

Antimicrobial prophylaxis with Ven-AZA

Preventing infection	Severe and prolonged neutropenia is common with these regimens, even after achieving remission. For patients with grade 4 neutropenia ($<0.5 \times 10^9$/L), antifungal prophylaxis according to institutional practice; if CYP3A4 inhibitors are used (eg, ciprofloxacin and/or azole antifungals), venetoclax dose adjustment is required (see optimizing venetoclax dosing) Hospitalization until hematologic recovery should be considered for selected patients with a high risk of complications or inadequate social support networks to enable safe outpatient management Treatment-related neutropenia may occur in the later part of the cycle and recover rapidly with commencement of G-CSF

DiNardo et al. How I treat. Blood. 2020

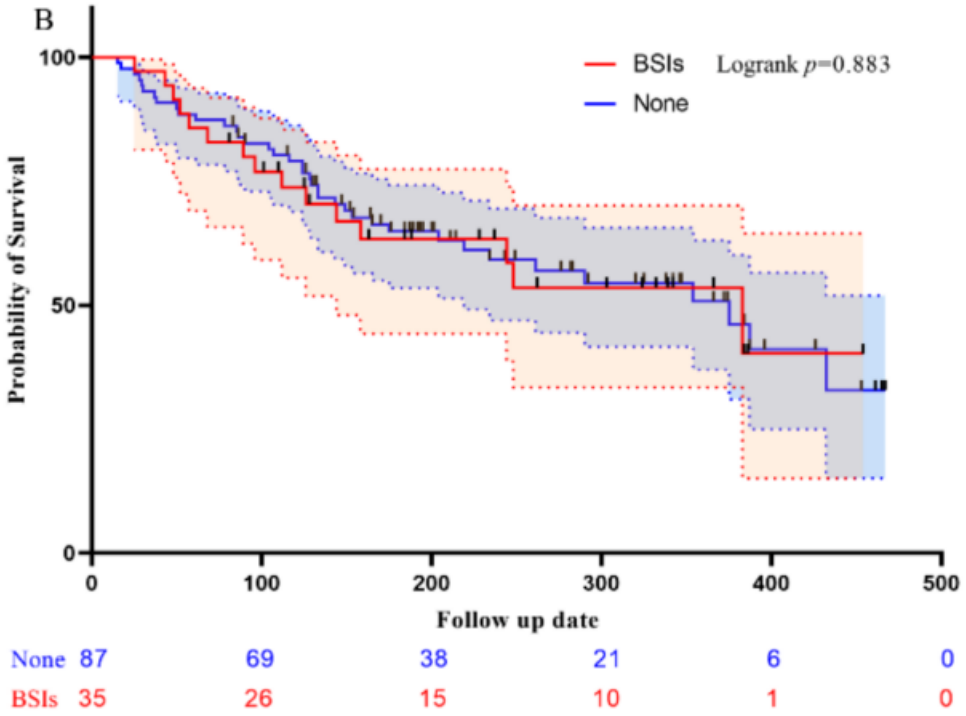
waiting to administer them, with the appropriate decrease in venetoclax dose, after the target dose has been achieved so as not to change the risks for or recognition of TLS. Regarding antiviral and antibacterial prophylaxis, we also acknowledge that there is widely variable institutional and personal practices and there is insufficient evidence reported from the venetoclax plus HMA clinical trial to mandate this [43]. Unlike azoles, most commonly used antiviral and antibacterial prophylactic agents do not require venetoclax dose adjustments.

Jonas B et al. Leukemia. 2019

CYP3A4: cytochrome P450 3A4; G-CSF: granulocyte-colony stimulating factor; TLS: tumor lysis syndrome; Ven-Aza: Venetoclax and Azacitidine.

What is the risk of infection?

Total no. bacterial infections	$N = 110$
Monomicrobial infections	62 (56.4)
Polymicrobial infections	11 (10)
Non-spectated infections[a]	37 (33.6)
Incidence of infection	$N = 235$
Bacteraemia	45 (19.1)
Pneumonia	25 (10.6)
Urogenital	22 (9.4)[b]
Extra-abdominal abscess	13 (5.5)
Intra-abdominal infection	5 (2.1)
Pathogen classification	
Gram-positive organisms	30
Coag-negative staphylococcus	6
Staphylococcus aureus	5
Streptococcus spp.	8
Enterococcus	6
Other	5
Gram-negative organisms	54
Enterobacteriaceae	41
Pseudomonas aeruginosa	4
Other	2
Infections in the setting of antibacterial prophylaxis	35 (31.8)
Fluoroquinolone	31 (88.6)
Third-generation cephalosporin	4 (11.4)
Cycles between VEN-HMA initiation and infection	
Cycle 1–2	65 (59.1)
Cycle 3–4	20 (18.2)
Cycle 5+	25 (22.7)



BSI: Bacterial Bloodstream Infections

Lee R et al. Cancers. 2021
On S et al. Br J Haematol. 2022

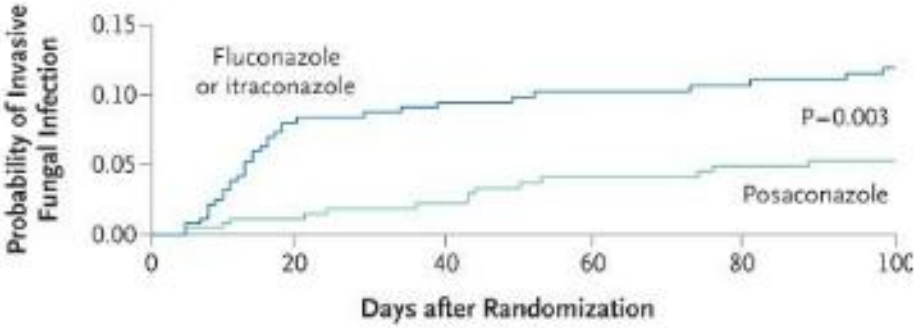
So what I do?

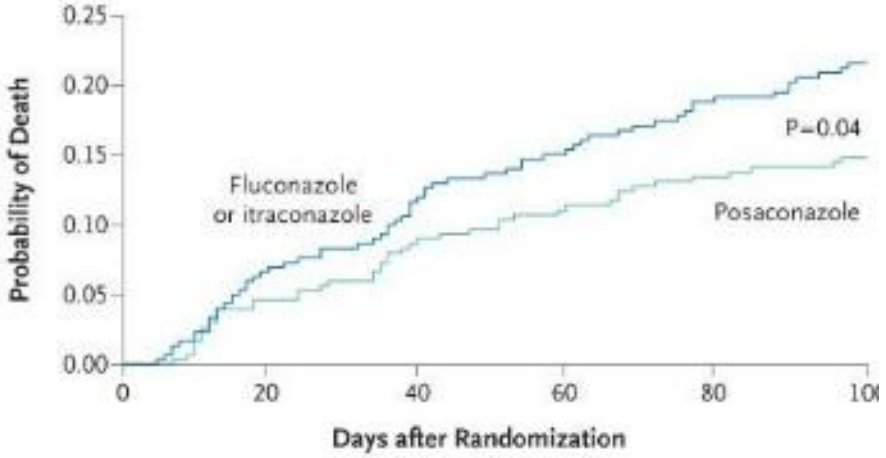
- I don’t deliver bacterial prophylaxis because
- Retrospective data shows no evidence of benefit.
- Prospective data show concern about the spread of MDR bacterial.
- We are in the era when we try to use less antibiotic (several + phase 2 studies and ongoing phase III SAFE study).

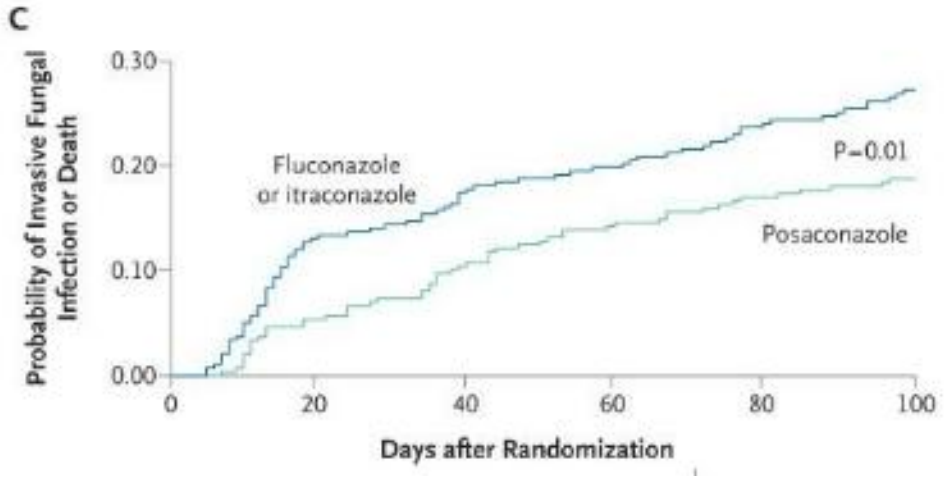
MDR: multidrug resistance.

EBM – fungal prophylaxis

- FIT AML patient : no longer a discussion







Cornely O et al.
NEJM.2007

AML: acute myeloid leukemia; EBM: Evidence-based medicine

EBM – fungal prophylaxis

- Unfit AML patient
- Recommended by ECIL
- Indicated by NICE UK guideline

BUT it remains one of the HOT topic in the field…

Majority of the data is retrospective.

One prospective data but results are difficult to believe.

So… What are evidences ?

AML: acute myeloid leukemia; EBM: Evidence-based medicine; ECIL: European Conference on Infections in Leukemia; NICE: national institute for clinical excellence

Is there IFI with Ven-Aza?

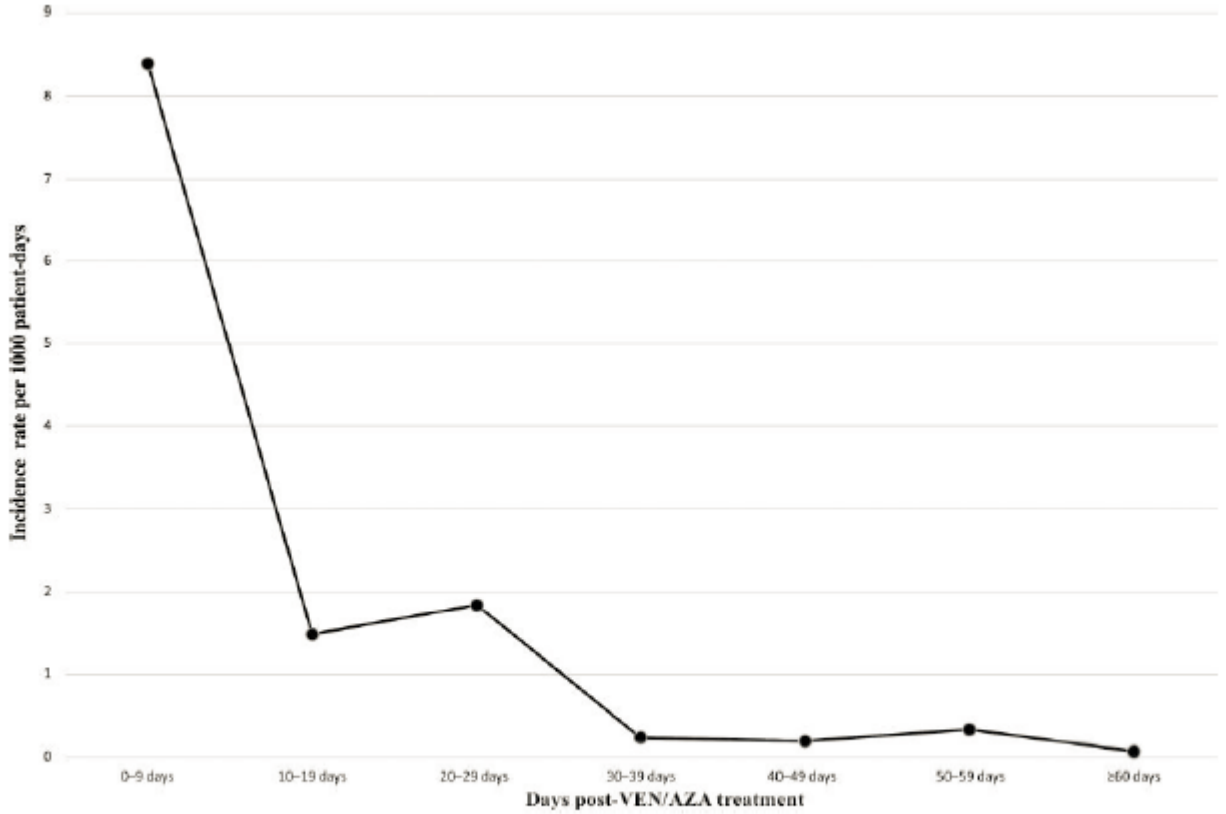
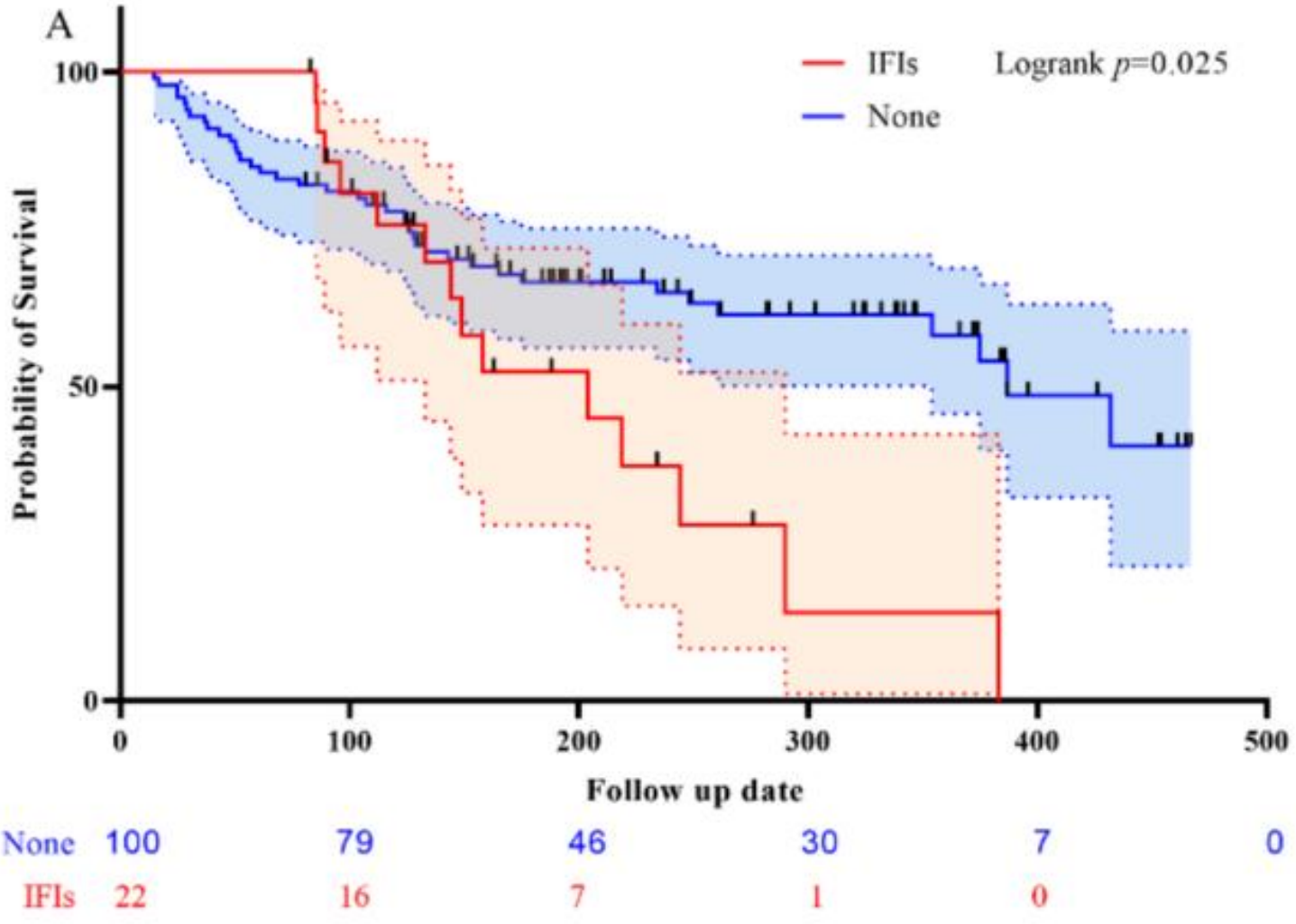


Figure 1. Incidence rate of invasive fungal infections (IFIs) after starting venetoclax/azacitidine (VEN/AZA) treatment. Patients diagnosed with proven, probable, and possible IFI were categorized by the number of days between starting VEN/AZA treatment and starting antifungal treatment.

IFI: invasive fungal infection; Ven/Aza: venetoclax and azacitidine

Zhang A et al. OFID. 2022

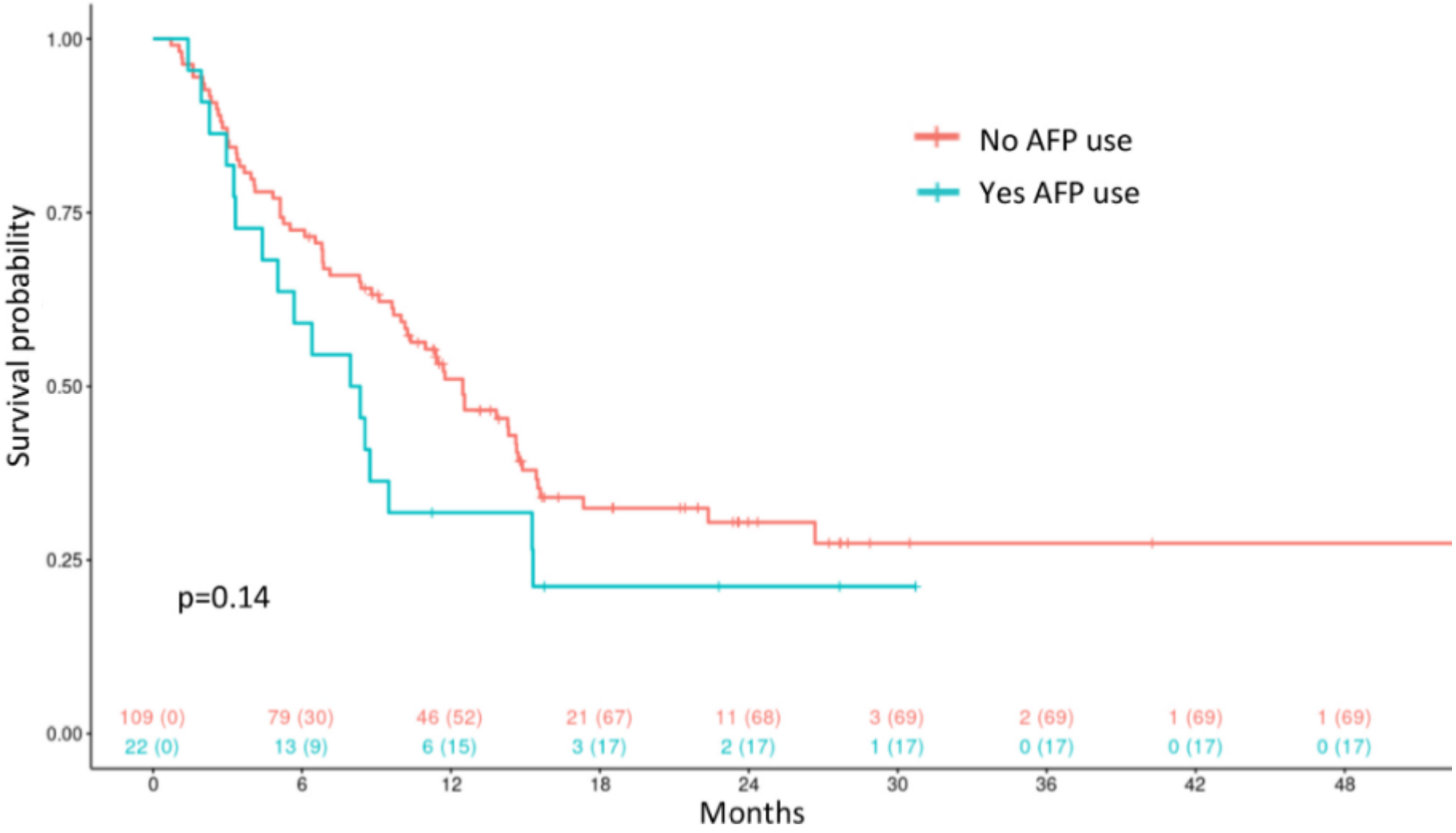
Is IFI a severe complication?



IFI: invasive fungal infection

Lee R et al. Cancers. 2021

Is the prophylaxis useful?



AFP: antifungal prophylaxis

Chen E et al. Leuk & lymph. 2022

Real data

Ref	Period	Nature of study	Site of the study	Number of patients	mAGE	ND AML	R/R AML	ELN Favorable	ELN Int	ELN Adverse
1	2014-2020	retrospective	monocentric (tertiary - Colorado)	144	72 (66-76)	100%	0%	17%	16%	64%
2	2016-2018	retrospective	monocentric (tertiary - CA)	119	69 (18-86)	46%	64%	11%	29%	60%
3	2016-2020	retrospective	multicentric (Californie)	235	68 (23-92)	55%	45%	na	na	na
4	2016-2021	retrospective	monocentric (tertiary Boston)	131	72 (22-89)	100%	0%	7,60%	20%	72%
5	2020-2021	retrospective Korea	monocentric (tertiary hospital)	122	61 (47-70)	32%	68%	20,5	37,7	51
	2014-2021			**751**						
6	2010-2020	retrospective	monocentric (tertiary)	98 AML (118 patients included)	NA	NA	NA	8,40%	30,30%	41,20%
7	2019-2020	Prospective	multicentric	132	73 (25-84)	NA	NA	NA	Na	Na

AML: acute myeloid leukemia; ELN Adv: European LeukemiaNet Adverse; ELN Int: ELN Intermediate; mAGE: median age; NA: not applicable; ND AML: newly diagnosed AML; R/R AML: Relapsed/Refractory AML

ref	n	Antifungal prophylaxis	mDura Proph	Type of prophylaxis	IFI	onset IFI	Proven/probable	under prophylaxis	fungal disease
1	144	10 (6,9%)	31 (9-63)	Anidulafungin (6) **Fluconazole (4)** isavuconazole (1)	25 (17%)	majority before day 60	8 (5,6%)	0	Aspergillosis
2	119	94 (79%)	Na	micafungin (45) posaconazole (25) isavuconazole (15) voriconazole (5)	15 (12,6%)	72 days (35-281)	7/8 (12,5%)	12/15 (mold prop)	7 aspergillus 5 mucor
3	235	158 (67,20%)	65 (1-195)	**Fluconazole (4)** posaconazole (29%) voriconazole (19%) isavuconazole (12%) echinocandins (5%)	30 (12,8%)	8/12 during first two-cyclus	7/5 (5,1%)	5+1/12	4 aspergillus 3 candida 2 mucor
4	131	17%	Na	**fluconazole (68%)** voriconazole (9,1%) posaconazole (9,1%) isavuconazole (14%)	17 (13%)	Na	3/1 (3%)	0	Candida aspergillus
5	122	88,50%	Na	fluconazole (98%) posaconazole (2%)	33 (27%)	55 (26-80)	2/20 (18%)	3 (mold prophylaxis)	aspergillus
	751	**(6,9-88,5)**			**120 (16%)**		**61 (8,1%)**		
6	98	66%	Na	Voriconazole (100%)	9		7 prob / 2 proven	8	Aspergillosis
7	132	not clearly reported		Voriconazole Posaconazole	18	majority during 3 first cycles	not clearly reported	not clearly reporter	Aspergillosis Candida

IFI: invasive fungal infection; mDura Proph: median duration of prophylaxis

1. Zhang A et al. OFID. 2022
2.Aldoss I et al. Blood Adv.2019
3. On S et al. Br J Haematol. 2022
4. Chen E et al. Leuk & lymph. 2022
5. Lee R et al. Cancers. 2021
6. Hall V et al. OFID.2023
7. Candoni A et al. Am J hemato. 2023

Real data

- Based on these data, some patients are more likely to present IFI :

1. R/R AML (2)
2. No response to therapy (2)
3. TP53 mutated (4)
4. Poor PS (4)
5. Therapy-related AML (5)

1.Zhang A et al. OFID. 2022. 2.Aldoss I et al. Blood Adv.2019 3. On S et al. Br J Haematol. 2022
4. Chen E et al. Leuk & lymph. 2022 5. Lee R et al. Cancers. 2021.
6. Hall V et al. OFID.2023 7. Candoni A et al. Am J hemato. 2023

AML: acute myeloid leukemia; IFI: invasive fungal infection; PS: performance status; R/R AML: Relapsed/Refractory AML

What I do?

- At the diagnostic

If patient is neutropenic, I start VenAza with posaconazole.

If patient is non neutropenic, I start only VenAza.

- After ANC recovery,

I stop with fungal prophylaxis

ANC: absolute neutrophil count; VenAza; venetoclax and azacitidine.

Why do I not deliver posaconazole for everybody?

- **Toxicity – side effect (1)**

Hepatotoxicity, QTc prolongation neurotoxicity

$\Rightarrow$14.7 % experiments toxicity (2)

$\Rightarrow$14% discontinued due to toxicity (3)

- **Drug-drug interaction**

May expose to under- or overexposure

- **Delay to recuperation**

Demonstrated for platelet recuperation (28 vs 22 days) for patient with azoles prophylaxis (4)

- **Increase resistance to azoles treatments (5)**

1. Chan S et al. Med.Mycol. 2020 2. Ostrosky-Zichner L. Infect. Dis. Thera. 2022
3.Rausch C. Clin. Infect. Dis. 2022 4. Rausch C et al . Cancer. 2021. 5 Lamoth F et al. Clin Infect Dis. 2017

QTc: QT corrected for heart rate

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39th General Annual Meeting of the Belgian Hematology Society

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face-to-face meeting

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THANK YOU

for your attention