Olgularla Hematoloji-Onkoloji

Hastalarında Antifungal Profilaksi

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Olgu 1:

48 y, erkek hasta, yeni tanı AML

Ek Hastalık: 60 paket/yıl sigara, KOAH hastası

Kemoterapi Cytarabin (200 mg/m^2/gün 7 gün) + Daunorubicin (90 mg/m^2 /gün 3 gün)

Hastaya IFI profilaksisi için inhaler L- Amfoterisin B (haftada 2 defa 10 mg) başlanıyor.

Bu hastada IFI riski yüksek midir?

Antifungal profilaksi gerekir miydi?

Profilaksi rejimi doğru mu?

AML-MDS remisyon indüksiyon tedavisi almakta olan hastalarda IFI riski:

(Flukonazol profilaksisi altında)

Candida sıklığı <%2 (0.15-1.55), IA sıklığı %5-24

17 Avrupa ülkesi için ortalama IA sıklığı %8.1

Clin Infect Dis 2015; 61: 324–31

http://hdl.handle.net/2078.1/145688

IFI Riskini Artıran Faktörler:

- Nötropeni, monositopeni
- İleri Yaş
- Pürin analoglarının kullanılması
- Mukozit
- Santral venöz kateter
- KOAH
- Mantar sporlarına maruziyet
- Refrakter Hastalık
- HEPA fitreli oda olmaması
- COVID-19, İnfluenza infeksiyonları

Haematologica 2015; 100: 284–92.

Ann N Y Acad Sci 2012; 1272: 23–30.

J Antimicrob Chemother 2018; **73**: 3221–3230
doi:10.1093/jac/dky286 Advance Access publication 1 August 2018

Journal of Antimicrobial Chemotherapy

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

Johan A. Maertens[1]*, Corrado Girmenia[2], Roger J. Brüggemann[3], Rafael F. Duarte[4], Christopher C. Kibbler[5],

IFI riski yüksek (>%8) olgularda primer profilaksi önerilir:

Table 3. ECIL recommendations on primary antifungal prophylaxis in adult patients with AML and MDS undergoing intensive remission-induction chemotherapy[a]

Antifungal agent	Grading	Comments
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	A-I	Recommended if baseline incidence of mould infections is high. Given the increased absorption of the tablet, it is likely that the need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis).
Fluconazole 400 mg q24h	B-I	Only recommended if the incidence of mould infections is low. Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach.
Itraconazole oral solution 2.5 mg/kg q12h	B-I	Recommended if baseline incidence of mould infections is high. May be limited by drug–drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations.
	B-II	Recommended if baseline incidence of mould infections is high. It is recommended to monitor serum drug concentrations.
All echinocandins	C-II	Insufficient data on efficacy and tolerability.
		fficient data on dose, frequency and duration, as well as on efficacy nd tolerability.
		fficient data on dose, frequency and duration, as well as on efficacy nd tolerability.
		when combined with fluconazole 400 mg q24h.

[a]Primary antifungal prophylaxis might be considered during intensified consolidation therapy (see text).

! Azol prf. antrasiklinler bittikten 24s sonra başlanmalı

! Ciddi mukozit ve ishal yoksa, (Posa tablet için) TDM gerekmez

! Konsolidasyon tedavisi alanlarda 1º prf önerilmez (IFI <%5)

! Standart MDS tedavisi alanlarda 1º prf önerilmez (IFI < %2)

! ALL'de Vinka alkoloidleri ile ciddi etkleşim nedeniyle önerilmez

! KLL, MM, Lenfoma, Myeloproliferatif Hst, Otolog nakilde önerilmez (IFI < %2)

Clinical and Experimental Medicine
https://doi.org/10.1007/s10238-023-01062-9

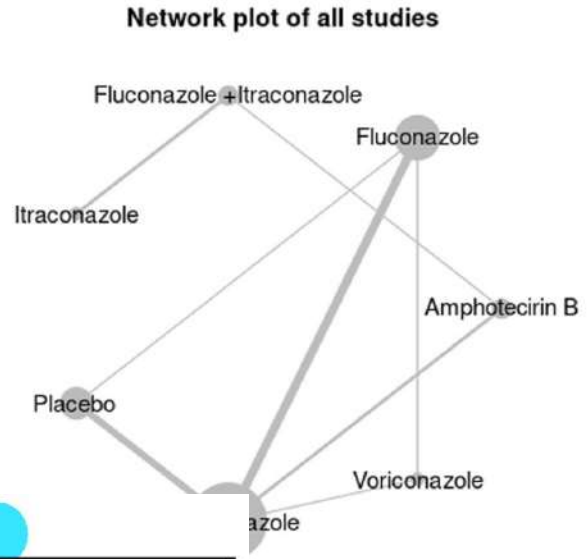
14/04/2023

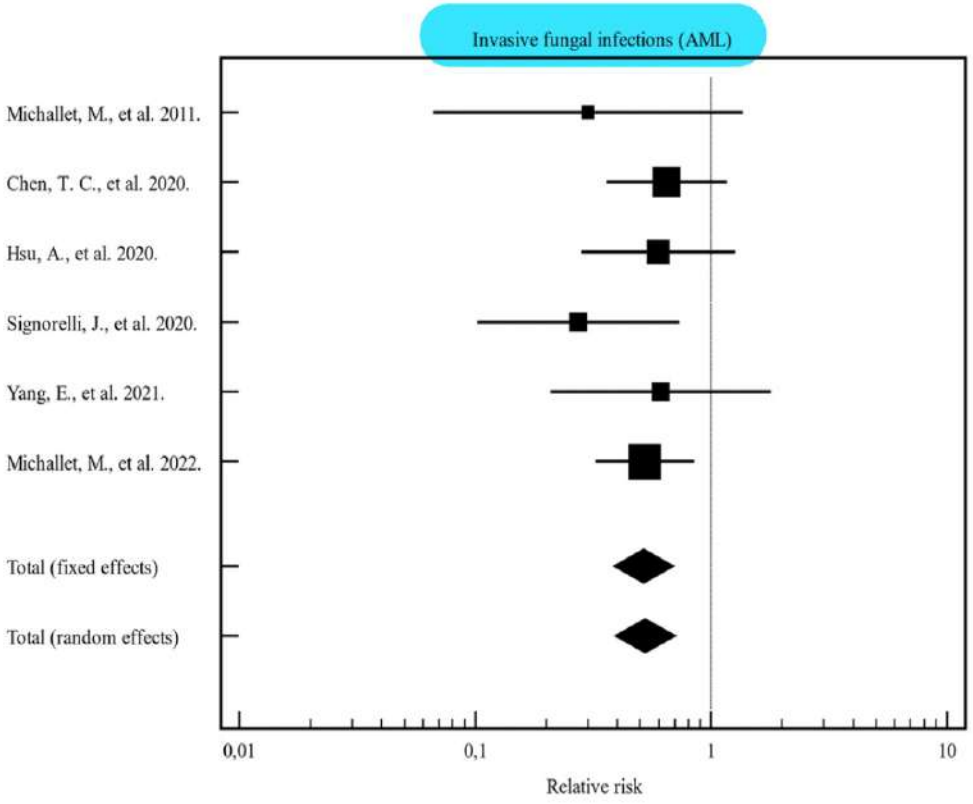
REVIEW

The impact of antifungal prophylaxis in patients diagnosed with acute leukemias undergoing induction chemotherapy: a systematic review and meta-analysis

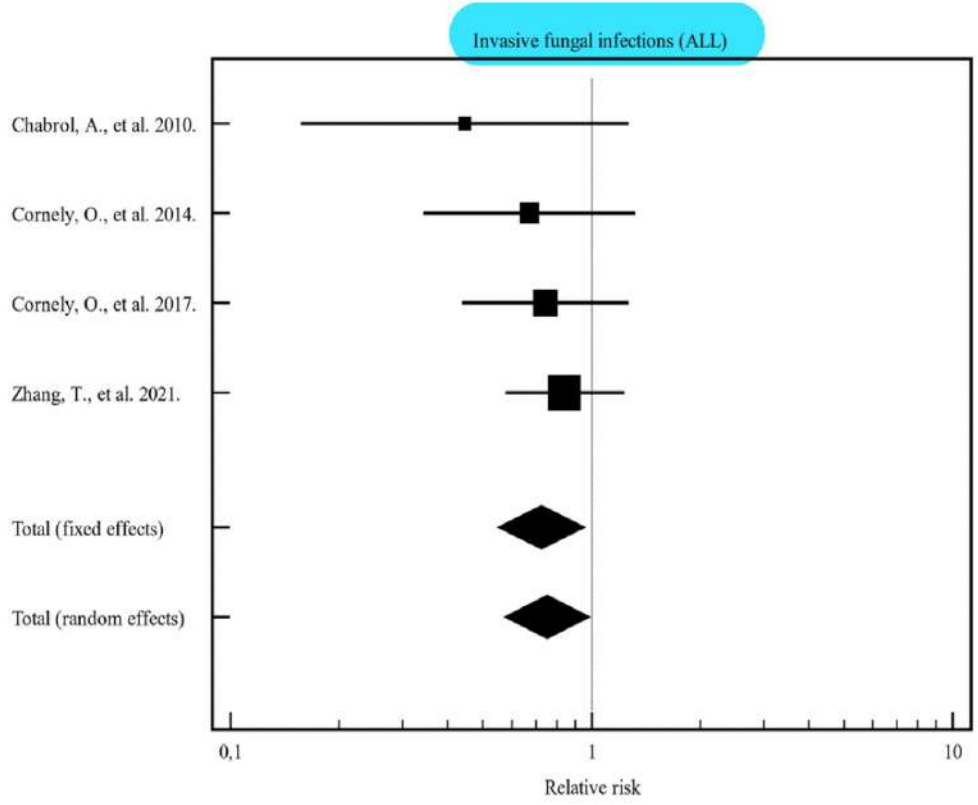
Luiz Ricardo Soldi[1,2,3] · Yasmin Nascimento Bernardes Coelho[1,3] · Luiz Renato Paranhos[1] · Marcelo José Barbosa Silva[1,2,4]

33 çalışmanın meta-analizi





Total of pooled random effects: (RR: 0.527 (95% CI: 0.391; 0.709). p<0.001.)



Total of pooled random effects: (RR: 0.753 (95% CI: 0.574; 0.988). p=0.041)

Olgu 2:

34 y, kadın hasta, AML Allo KHN planlanıyor (Tam uyumlu kardeşten)

Ek Hastalık: Yok

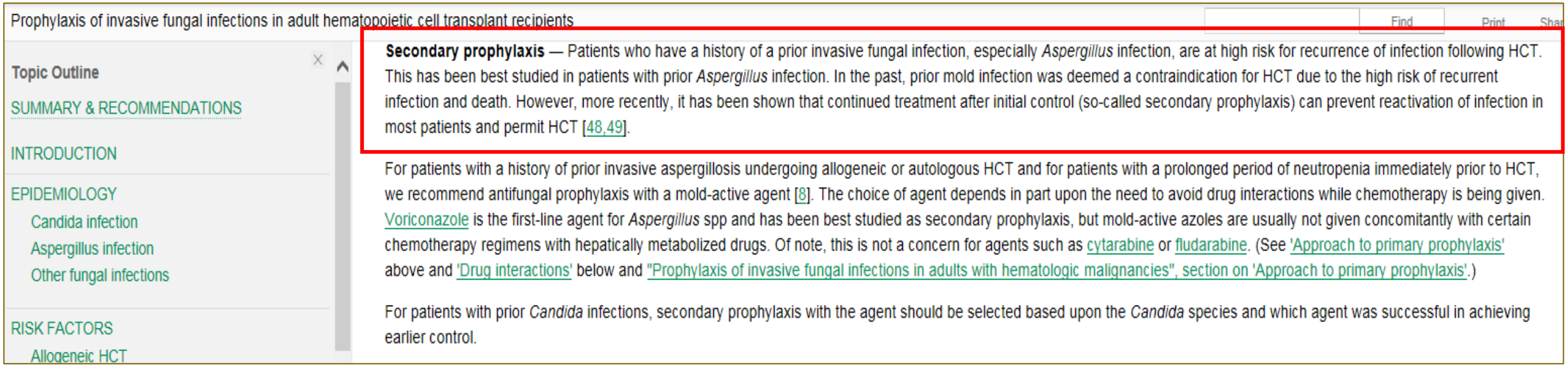
Remisyon indüksiyon sırasında İA tespit edilmiş, Vorikonazol ile tedavi edilmiş

Bu hastada IFI riski yüksek midir?

Antifungal profilaksi gerekir mi?

Hangi ilaç?

Sekonder profilaksi



Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients

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Topic Outline

SUMMARY & RECOMMENDATIONS

INTRODUCTION

EPIDEMIOLOGY

Candida infection

Aspergillus infection

Other fungal infections

RISK FACTORS

Allogeneic HCT

Secondary prophylaxis — Patients who have a history of a prior invasive fungal infection, especially *Aspergillus* infection, are at high risk for recurrence of infection following HCT. This has been best studied in patients with prior *Aspergillus* infection. In the past, prior mold infection was deemed a contraindication for HCT due to the high risk of recurrent infection and death. However, more recently, it has been shown that continued treatment after initial control (so-called secondary prophylaxis) can prevent reactivation of infection in most patients and permit HCT [48,49].

For patients with a history of prior invasive aspergillosis undergoing allogeneic or autologous HCT and for patients with a prolonged period of neutropenia immediately prior to HCT, we recommend antifungal prophylaxis with a mold-active agent [8]. The choice of agent depends in part upon the need to avoid drug interactions while chemotherapy is being given. Voriconazole is the first-line agent for *Aspergillus* spp and has been best studied as secondary prophylaxis, but mold-active azoles are usually not given concomitantly with certain chemotherapy regimens with hepatically metabolized drugs. Of note, this is not a concern for agents such as cytarabine or fludarabine. (See 'Approach to primary prophylaxis' above and 'Drug interactions' below and "Prophylaxis of invasive fungal infections in adults with hematologic malignancies", section on 'Approach to primary prophylaxis'.)

For patients with prior *Candida* infections, secondary prophylaxis with the agent should be selected based upon the *Candida* species and which agent was successful in achieving earlier control.

Önceki yıllarda aspergilloz öyküsü –yüksek tekrarlama riski nedeniyle- HKHN için kontrindikasyon olarak kabul edilmekte idi; sekonder profilaksi reaktivasyonu engellediği için nakil yapılabilir hale geldi

Clinical Infectious Diseases Advance Access published June 29, 2016

Clinical Infectious Diseases

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Evidence Summary. Patients with malignancy and IA frequently require additional antineoplastic therapy and/or HSCT. The major concern is that aspergillosis will progress during subsequent periods of immunosuppression. Several studies have shown that IA is not a contraindication for additional treatment, including HSCT [367, 388–391]. It is important to administer mold-active antifungal treatment during subsequent periods of immunosuppression (referred to as secondary prophylaxis) to avoid recurrence or progression. In a multicenter retrospective survey of patients with pretransplant aspergillosis, 27 of 129 patients developed progressive fungal disease following allogeneic HSCT. The variables that increased the 2-year cumulative incidence of aspergillosis progression were longer duration of neutropenia after transplantation, refractory malignancy, and <6 weeks from start of antifungal therapy and HSCT [389]. In a prospective, multicenter trial of voriconazole as secondary prophylaxis in patients with pretransplant IFIs (the majority were aspergillosis), the one-year cumulative incidence of invasive fungal disease was 7% following allogeneic HSCT [367].

Çok merkezli bir çalışmada IA öyküsü olan 27/129 allo KHN alıcısında İA tekrarlamış (%21)

Çok merkezli başka bir çalışmada IA öyküsü olan allo KHN alıcılarında vorikonazol prf ile İA sıklığı: %7

Ann Hematol (2016) 95:1435–1455
DOI 10.1007/s00277-016-2711-1

ORIGINAL ARTICLE

Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016

Andrew J. Ullmann[1] · Martin Schmidt-Hieber[2] · Hartmut Bertz[3] · Werner J. Heinz[1] · Michael Kiehl[4] · William Krüger[5] · Sabine Mousset[6] · Stefan Neuburger[7] · Silke Neumann[8] · Olaf Penack[9] · Gerda Silling[10] · Jörg Janne Vehreschild[11] · Hermann Einsele[1] · Georg Maschmeyer[12] · on behalf of the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the DAG-KBT (German Working Group for Blood and Marrow Transplantation)

Antifungal prophylaxis in allo-HCT

Invasive fungal diseases (IFDs) are severe complications associated with prolonged hospital length of stay, costs, long-term treatment, and high mortality [94]. Approximately two thirds of the IFD develop in allo-HCT patients after leukocyte recovery [95, 96]. Furthermore, intensifying immunosuppression for treatment of transplant rejection or GvHD and CMV infection impose an imminent risk for IFD [97, 98].

The incidence of invasive aspergillosis (IA) varies between reports and may reach 23 % [94, 99]. Primary prophylaxis is highly recommended since diagnostic tools do not present with sufficient sensitivity numbers. This is mirrored in studies with a significant number of post-mortem diagnoses of fungal diseases [100–102]. In patients diagnosed with IA, mortality rates of up to 60 % have been reported despite adequate treatment [103]. Secondary prophylaxis is recommended prior to allo-HCT **(BII)** [104].

Table 2 Antifungal prophylaxis

Intention	Intervention	SoR	QoE	Comments
Prevent mould infection in patients without GvHD, day 1–100	Voriconazole 200 mg bid oral or iv[b]	C	I	No difference seen in the trial in comparison to fluconazole
	Posaconazole (suspension) 200 mg tid[b]	B	II_t	Improved overall survival in AML/MDS induction during neutropenia, new formulations (tablet and iv, 300 mg qid) provide a better bioavailability
	Micafungin 50 mg/day	C	I	Only during neutropenia, morbidity advantage
	Itraconazole suspension 2.5–7.5 mg/kg or capsules	C	I	Administered up to 180 days if GVHD was diagnosed; higher toxicity in comparison to fluconazole, TDM: cutoff at 500 mg/mL (AII
Prevent invasive *Candida* disease in patients without GvHD, day 1–100	Fluconazole 400 mg/day	A	I	Improved survival, note rising incidence of resistant *Candida* species since studies were published
	Voriconazole 200 mg bid oral or iv[b]	B	II_t	Also active against moulds, but no difference seen in the trial between voriconazole and fluconazole
	Posaconazole (suspension) 200 mg tid[b]	B	II_t	Also effective against moulds, new formulations (tablet and iv, 300 mg qd) provide a better bioavailability
	Micafungin 50 mg/day	B	II_t	Also effective against moulds, only during neutropenia, morbidity advantage
	Itraconazole suspension 2.5–7.5 mg/kg or capsules[b]	C	I	See above
Prevent invasive Aspergillosis during GvHD	Posaconazole (suspension) 200 mg tid[b]	A	I	improved survival (lower attributable mortality), new formulations (tablet and iv, 300 mg qd) provide a better bioavailability
Prevent fungal disease relapse (previous IFD)	Voriconazole[b]	B	II	considered as secondary antifungal prophylaxis, dosages as above
	Caspofungin, posaconazole	B	III	
Prevent fungal diseases[a]	Amphotericin B deoxycholate	D	II	Inacceptable toxicity

Ann Hematol (2016) 95:1435–1455

TDM önerileri ECIL-6 Kılavuzu

Triazol	Plazma Aralığı	Öneri Düzeyi	Ne zaman bakılması gerekir
Posakonazol	Profilaksi >0.7 mg/L Tedavi > 1 mg/L	BII (Etkinlik) AII (Etkinlik)	Süspansiyon :5-7 gün Tablet/i.v.: 3 gün
Vorikonazol	Profilaksi ve tedavi Kabul edilebilir: 1-6 mg/L Optimal: 2-5 mg/L	AII (Etkinlik) AII (Toksisite)	2-5 gün sonra Tekrarlama önerilir
İtrakonazol	Profilaksi : 0.5-4mg/L Tedavi: 1-4 mg/L	AII (Etkinlik) BII (Toksisite)	7-15 gün

Lewis R et al. ECIL 6 Meeting . September 2015, France.

Posakonazol

Notes:

- Where possible, Posaconazole tablets should be used in preference to the suspension because the tablets have a higher bioavailability.
- The suspension is not interchangeable with the tablets on a milligram-for-milligram basis, consult a pharmacist for advice.
- Posaconazole has the potential for a number of drug interactions, consult a pharmacist for advice.
- For intravenous formulation, the vehicle can accumulate in patients with moderate or severe renal impairment (creatinine clearance<50mg/ml), therefore renal function should be monitored closely.
- In the setting of possible malabsorption or other drug interaction, please discuss with microbiology
- *Therapeutic drug monitoring (TDM) for Posaconazole is not recommended.*

Ye et al. BMC Infectious Diseases (2022) 22:465
https://doi.org/10.1186/s12879-022-07442-y

BMC Infectious Diseases

RESEARCH Open Access

Posaconazole oral suspension for secondary antifungal prophylaxis in allogeneic stem cell transplantation recipients: a retrospective study

Peipei Ye, Renzhi Pei, Youqian Hu, Dong Chen, Shuangyue Li, Junjie Cao, Fenglin Li, Mengjie Wu, Ying Fang and Ying Lu*

Çin, retrospektif, 2016-2021
AKHN yapılıp Posakonazol kullanan 123 hasta
Önceden IFI: 30 hasta (%25) 180 gün prf uygulanıyor
7'si nakile aktif IFI ile alınıyor (yüksek doz Posa alıyor)
IFI olmayan 93 hasta, 90 gün prf alıyor

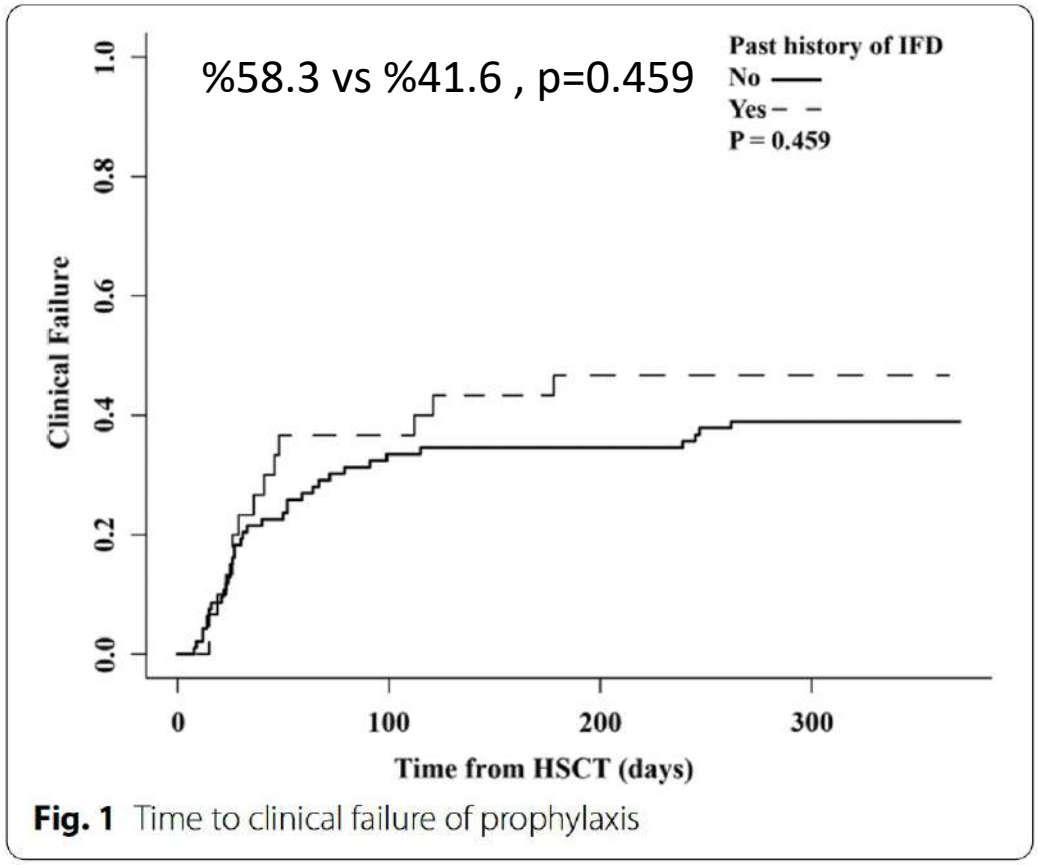

Fig. 1 Time to clinical failure of prophylaxis

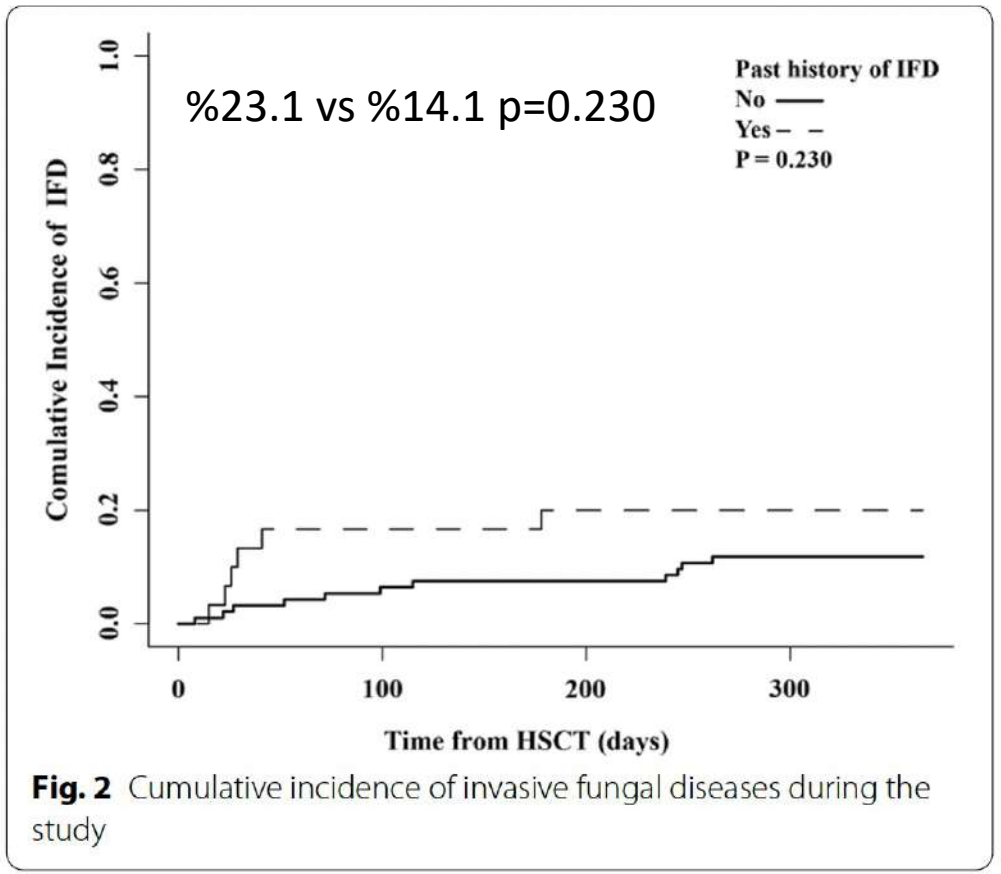

Fig. 2 Cumulative incidence of invasive fungal diseases during the study

Profilaksi süresi

Duration — The duration of antifungal prophylaxis should be individualized based on the patient's clinical status and history of prior fungal infections. The following general principles can be used to help determine the appropriate duration of prophylaxis:

- In allogeneic HCT recipients who do not have GVHD, prophylaxis against *Candida* spp is continued either until engraftment or for up to 75 days following transplantation, which in one trial was associated with continued benefit after engraftment [8,10,32].
- The optimal duration of antifungal prophylaxis in allogeneic HCT recipients with GVHD has not been defined [24]. In general, prophylaxis should be continued during the period of peak immunosuppression (eg, glucocorticoid equivalent of ≥1 mg/kg per day of prednisone for more than two weeks or addition of other anti-GVHD therapies for refractory GVHD) [30]. In such patients, we continue anti-mold prophylaxis until substantial doses of immunosuppressants (especially glucocorticoids) are no longer required. As an example, we suggest stopping once the dose of prednisone drops below 20 mg every other day, but the optimal duration has not been formally studied.
- In patients who have a history of a prior invasive fungal infection who are receiving secondary prophylaxis following HCT, prophylaxis is usually continued until discontinuation of immunosuppressive therapy. In such patients, follow-up imaging (CT scan of the organ involved in prior infection) and fungal markers (eg, *Aspergillus* galactomannan antigen, beta-D-glucan) are often obtained two to four weeks after antifungal prophylaxis has been discontinued to ensure that reactivation has not occurred.

Sekonder profilaksi:

- Nakil sonrası immünsüpresif tedavi kesilinceye kadar
- Sekonder profilaksi kesildikten 2-4 hafta sonra kontrol

Antifungal profilaksi

Antifungal Prophylaxis

Agent	Spectrum	Dosing	Dose Adjustment	CYP Drug Interactions	Adverse Effects
Caspofungin	• Active against Candida spp • Some activity against Aspergillus spp • Not active against dimorphic fungi, Mucorales, Cryptococcus spp.	70 mg IV x1 load, then 50 mg daily	None	None	Well tolerated
Fluconazole	• Active against most Candida spp; variable activity against C. glabrata; no activity against C. krusei • Active against Coccidioides, Cryptococcus spp	400 mg PO/IV daily	Renal	Inhibits 3A4 (moderate), 2C9 (moderate), 2C19 (strong)	Well tolerated, increased LFTs
Isavuconazole	Similar to posaconazole	372 mg PO/IV q8h x6 load, then 372 mg daily	None	Inhibits 3A4 (moderate) Substrate of 3A4	Similar to posaconazole, except shortens QTc
Liposomal amphotericin B	• Broad-spectrum antifungal activity • Not active against A. terreus, Candida lusitaniae, Lomentospora	3-5 mg/kg IV daily (adjusted body weight in obese)	None	None	AKI, hypokalemia, hypomagnesemia, infusion reactions (fever, chills, rigors, hypotension)
Posaconazole	• Active against Candida spp, Aspergillus spp • Some activity against Mucorales, Cryptococcus spp, dimorphic fungi	300 mg PO/IV q12h x2 load, then 300 mg daily*	None	Inhibits CYP3A4 (strong)	Increased LFTs, prolonged QTc, headache, rash, hypokalemia
Voriconazole	• Similar to posaconazole, except not active against Mucorales • Preferred agent for Scedosporium	400 mg PO q12h x2 load, then 200 mg q12h** 6 mg/kg IV q12h x2 load, then 4 mg/kg q12h (AdjBW in obese) **	Hepatic No renal dose adjustment	Inhibits CYP3A4 (strong), 2C19 (moderate) Substrate of CYP 2C19	Visual disturbances, hallucinations, photosensitivity, rash, increased LFTs, prolonged QTc, rare cases of skin malignancies (long-term use)

*Oral delayed-release tablet preferred and taken with food (oral suspension: not interchangeable with tablets, interpatient variability, consider therapeutic drug monitoring)
**Therapeutic drug monitoring recommended for all patients

Original Date: 12/10/2020 **ICHS Committee approved:** 09/14/2020 **ABX Subcommittee approved:** 09/17/2020 **Hematology/Oncology Faculty approved:** 12/11/2020
Authors: Edna Cheung, PharmD BCOP; William Alegria, PharmD BCIDP Gabriel Mannis, MD

KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Bilimle Sağlıkla 37.YIL