Hematoloji Bakış Açısı ile IFI Profilaksisinde Posakonazol'ün Yeri

Doç Dr Güldane CENGİZ SEVAL
Ankara Üniversitesi Tıp Fakültesi Hematoloji Bilim Dalı

65 yaş erkek hasta

- Yeni tanı standart risk AML
- ‘Aza+Ven’ indüksiyon kemoterapisi başlanacak
- Özgeçmiş:KOAH
- Remisyon elde edilir ise Alloejeneik HKHN planı var
- IFI risk??

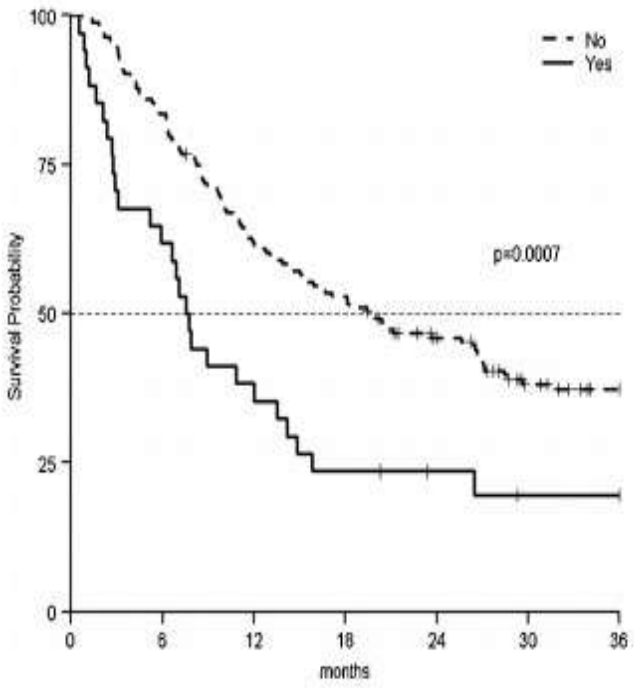
Hematolojik malignensilerde IFI…

- Mortaliteyi artırır.
- KT ve kök hücre naklini geciktirir.
- Hastanede yatışı uzatır.
- Artmış tedavi maliyeti getirir.

IFI ile remisyon ilişkisi

Probability of CR achievement.

Parameter	Odds ratio	95% confidence interval	*P*
Univariate analysis			
Hematologic Institution			
PTV vs PUI	1.99	0.91–4.35	0.08
Age			
≤60 years vs >60 years	3.24	1.58–6.62	0.001
Gender			
Female vs male	2.51	1.17–5.36	0.02
Secondary AML			
No vs yes	1.76	0.79–3.94	0.17
Performance status			
0–1 vs 2–3	6.56	2.91–14.78	<0.0001
WBC count			
≤50.000 vs >50.000	1.22	0.54–2.73	0.63
Genetic risk			
Favorable vs adverse	2.14	0.43–10.53	0.15
Intermediate vs adverse	0.50	0.22–1.11	0.02
Proven probable IFD			
No vs yes	4.39	1.97–9.77	0.0003
Multivariate analysis			
Age			
≤60 years vs >60 years	3.19	1.45–7.03	<0.0001
Performance status			
0–1 vs 2–3	5.42	2.30–12.81	<0.0001
Proven probable IFD			
No vs yes	4.09	1.71–9.81	<0.0001



Girmenia C,Leuk Res 2014

IFI saptanan hastada tedavi planı değişebilir.

- Bir sonraki kemoterapi planı %57 gecikme.
- Ortanca 11(1-38) gün.
- %68'inde tedavi planında bir değişiklik yapılmış.

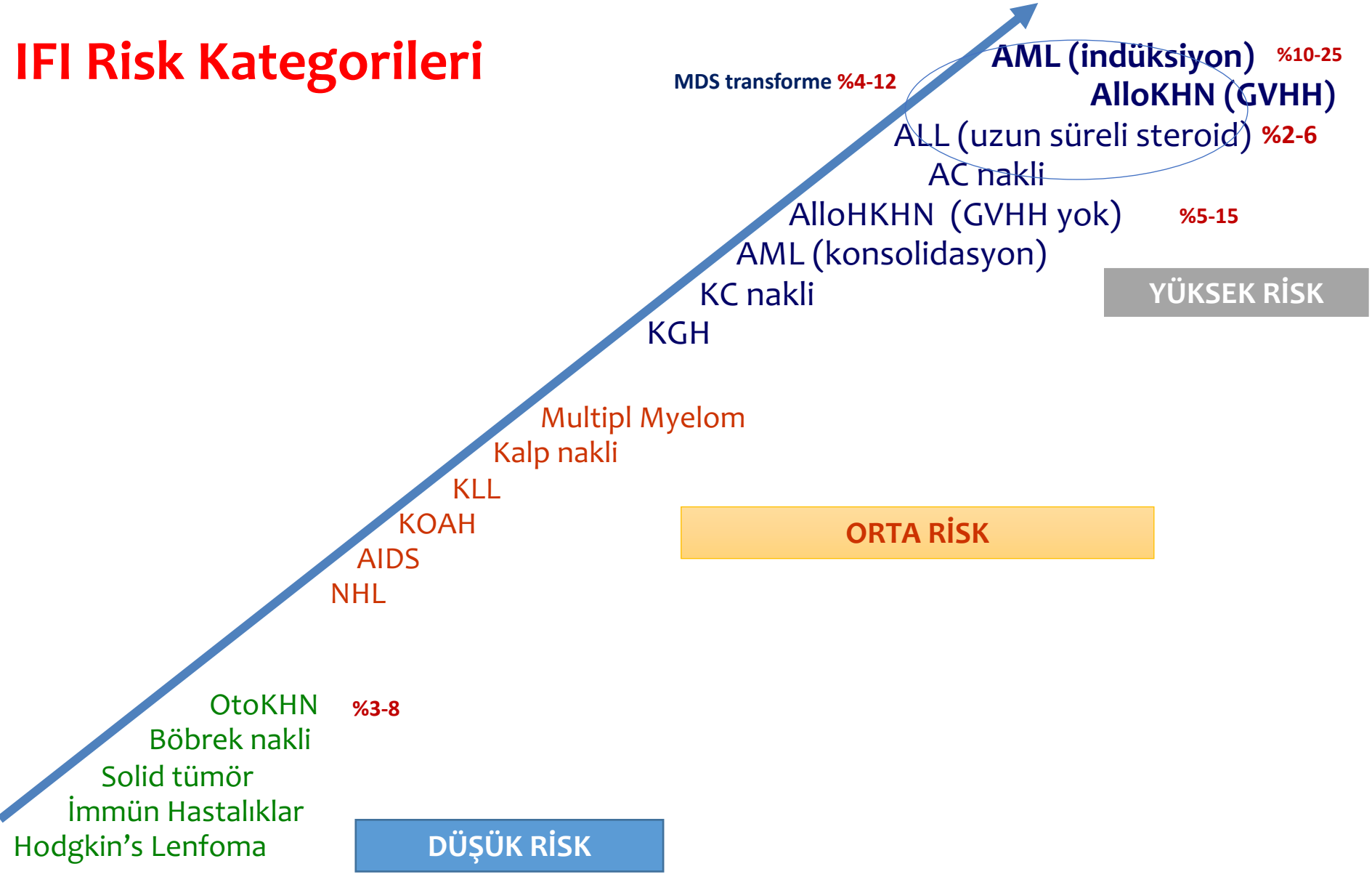
Even C, Haematologica 2011

Hematolojik malignenside IFI riskini belirleyen faktörler

HASTA KAYNAKLI	HASTALIK KAYNAKLI	TEDAVİ KAYNAKLI	MANTARA MARUZİYET
->65 yaş -Yüksek komorbidite -Aktif sigara içiciliği -KOAH -Immunite polimorfizm	-Tam remisyon elde edilme riskinin düşük olması -7günden uzun neu>500/mm3 -Lösemi durumu (Relaps/refrakter > indüksiyon > konsolidasyon) -İndüksiyon sonunda TR olmaması -15.Günde K.İ'nde blast bulunması	-Neu<100/mm3 >10 gün -Yüksek mukotoksik tedavi ->7 gün grade 3-4 mukozit	-Hepafiltreli odalar -Inşaat -Yüksek maruziyetli meslekler -Aspergillus öylüsü -Kandida kolonizasyonu

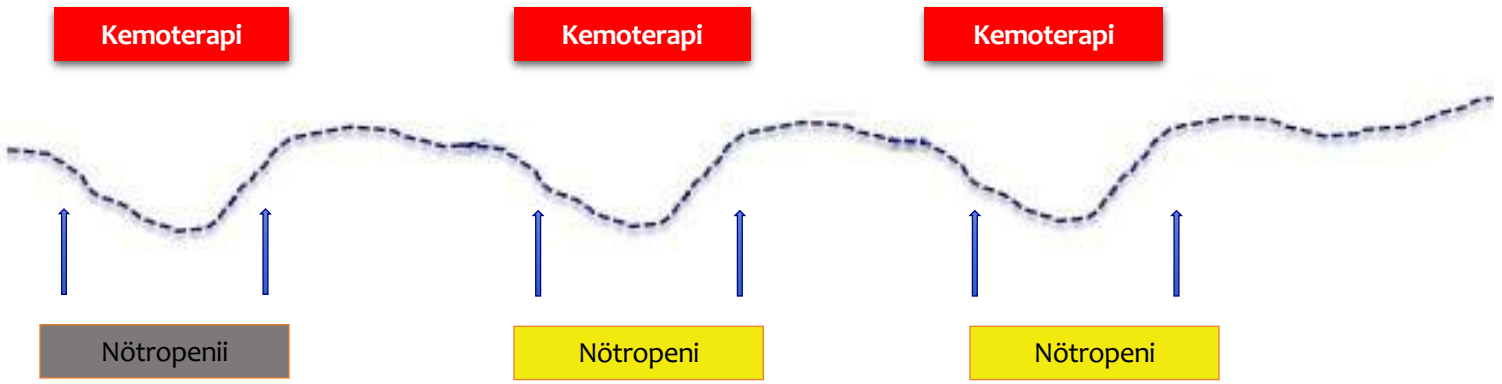
Pagano L, Blood Rev 2017

IFI Risk Kategorileri

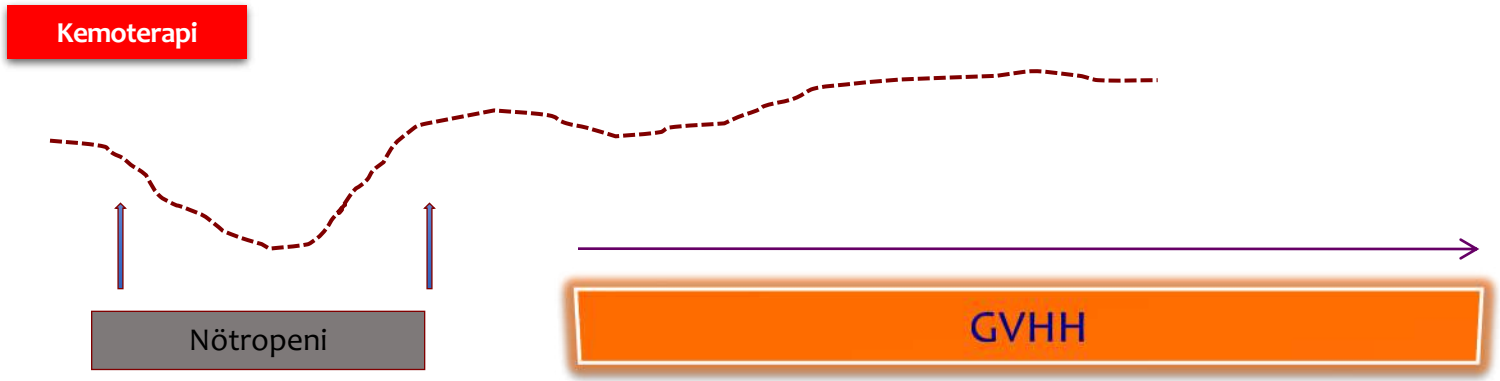


Pagano et al, J Antimicrob Chemother, 2011
Herbrecht et al, Ann N Y Acad Sci. 2012

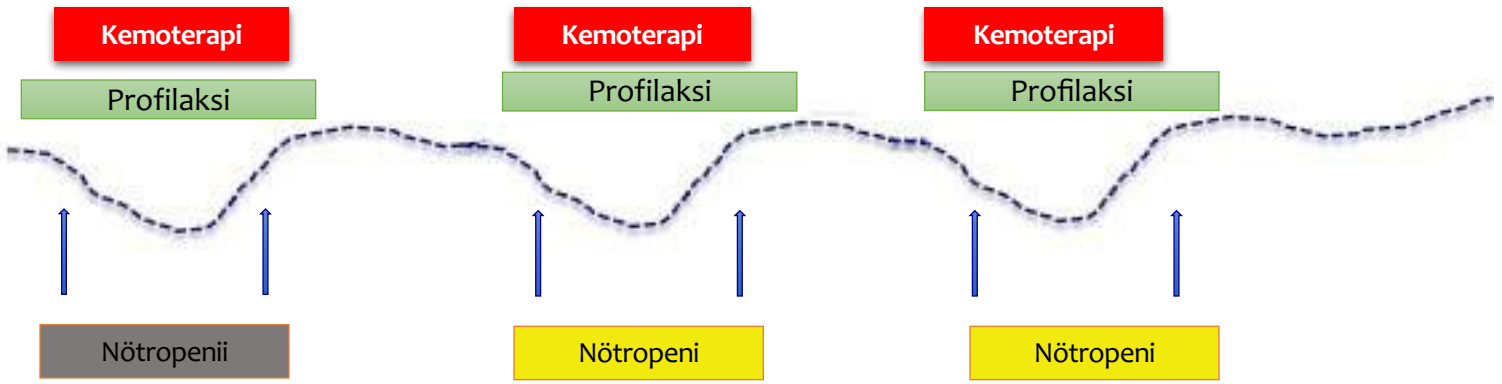
AKUT LÖSEMİ-YÜKSEK RİSKLİ MDS



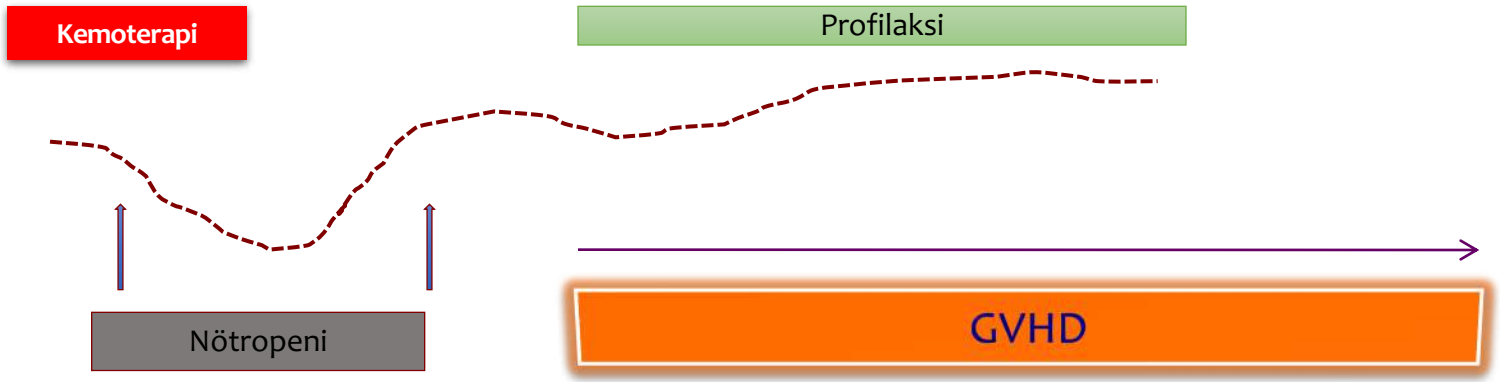
ALLOJENEİK HKHN



AKUT LÖSEMİ-YÜKSEK RİSKLİ MDS



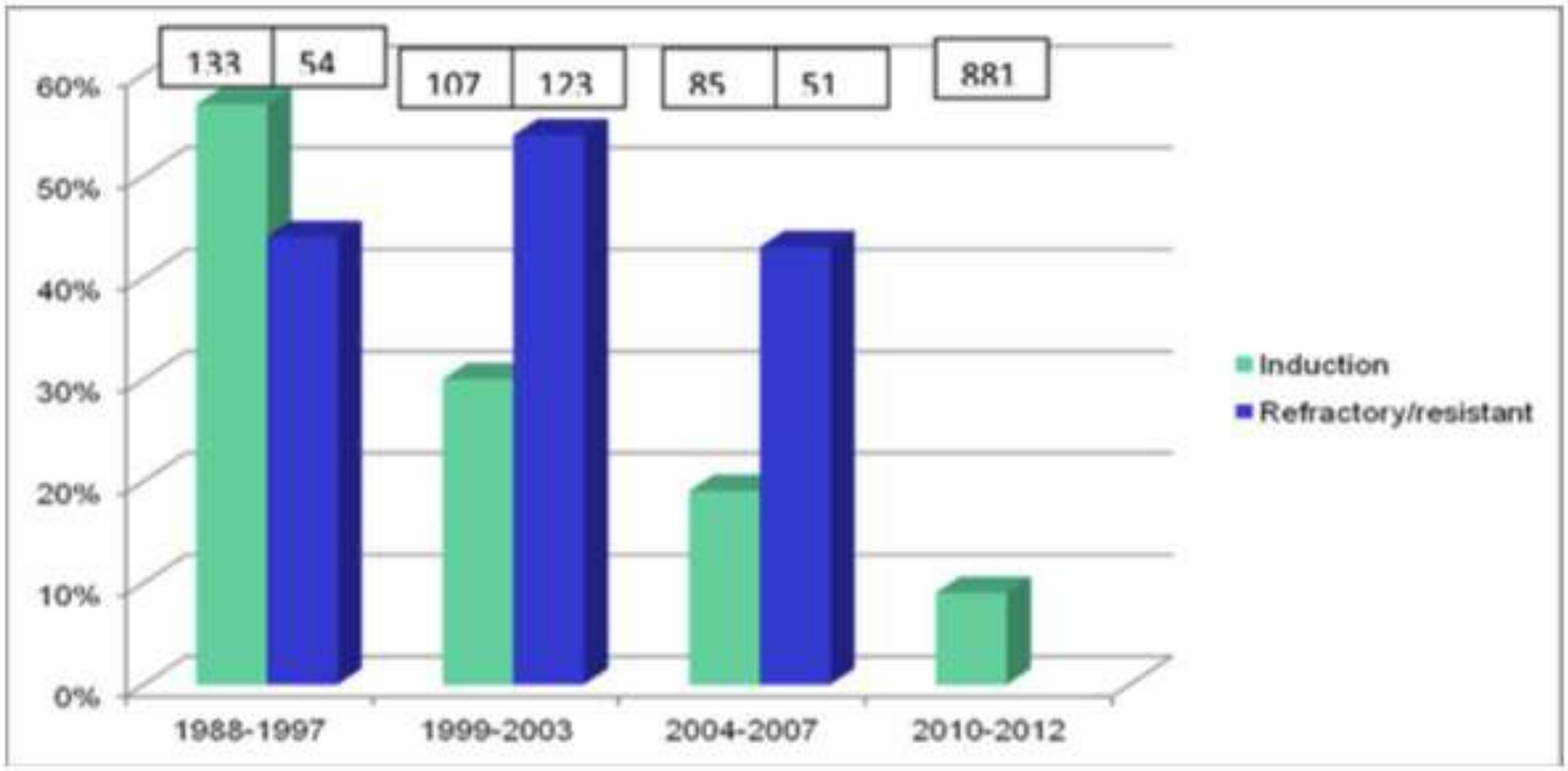
ALLOJENEİK HKHN



AML'de primer antifungal profilaksi

First author, citation and year	Setting	Design of the study (number of patients included in each arm)	Percentage of IFD		Absolute risk reduction of IFD	Percentage of deaths		Absolute risk reduction of death
			control group	experimental group		control group	experimental group	
Winston *et al.*[10] 1993	AML	Placebo ($n = 132$). Fluconazole oral 400 mg q24h or iv 200 mg q12h ($n = 123$).	8	4	0.04	3	1	0.02
Menichetti *et al.*[11] 1999	AML Autologous HSCT	Placebo ($n = 204$). Itraconazole oral solution 2.5 mg/kg q12h ($n = 201$).	4	2	0.02	9	7	0.02
Rotstein *et al.*[28] 1999	AML/MDS Autologous HSCT	Placebo ($n = 151$). Fluconazole oral 400 mg q24h ($n = 153$).	21	6	0.15	10	10	0.00
Harousseau *et al.*[27] 2000	AML/MDS	Placebo plus amphotericin B 2g q24h ($n = 276$).	5	3	0.02	8	6	0.02
	Autologous HSCT	Itraconazole oral solution 2.5 mg/kg q12h plus placebo ($n = 281$).						
Glasmacher *et al.*[26] 2006	AML	Fluconazole oral 400 mg q24h ($n = 246$).	2	2	0.0	3	2	0.01
	Autologous HSCT	Itraconazole oral solution 2.5 mg/kg q12h ($n = 248$).						
Cornely *et al.*[13] 2007	AML/MDS	Fluconazole oral 400 mg q24h or itraconazole oral solution 200 mg q12h ($n = 298$).	8	2	0.06	22	16	0.06
		Posaconazole oral suspension 200 mg q8h ($n = 304$).						

Yıllar içinde AML'de IFI'ye bağlı mortalite azalıyor…



Dragonetti C,Med Mycol 2016

MDS’de fungal infeksiyon riski

-Nötropeni

-Fonksiyonel nötrofil bozukluğu

Bakterisidal,Fungosidal etki bozuk,
CD11b/CD18 kompleks eksp.bozuk,
MPO,lizozim,laktoferrin ,Elastaz,Katepsin fonk. Anomali

-T,B,Treg,NK hücre disfonksiyonu

İleri yaş
Komorbiditeler
Demir yükü

MDS'de fungal infeksiyon riski
-hipometile edici tedaviler-

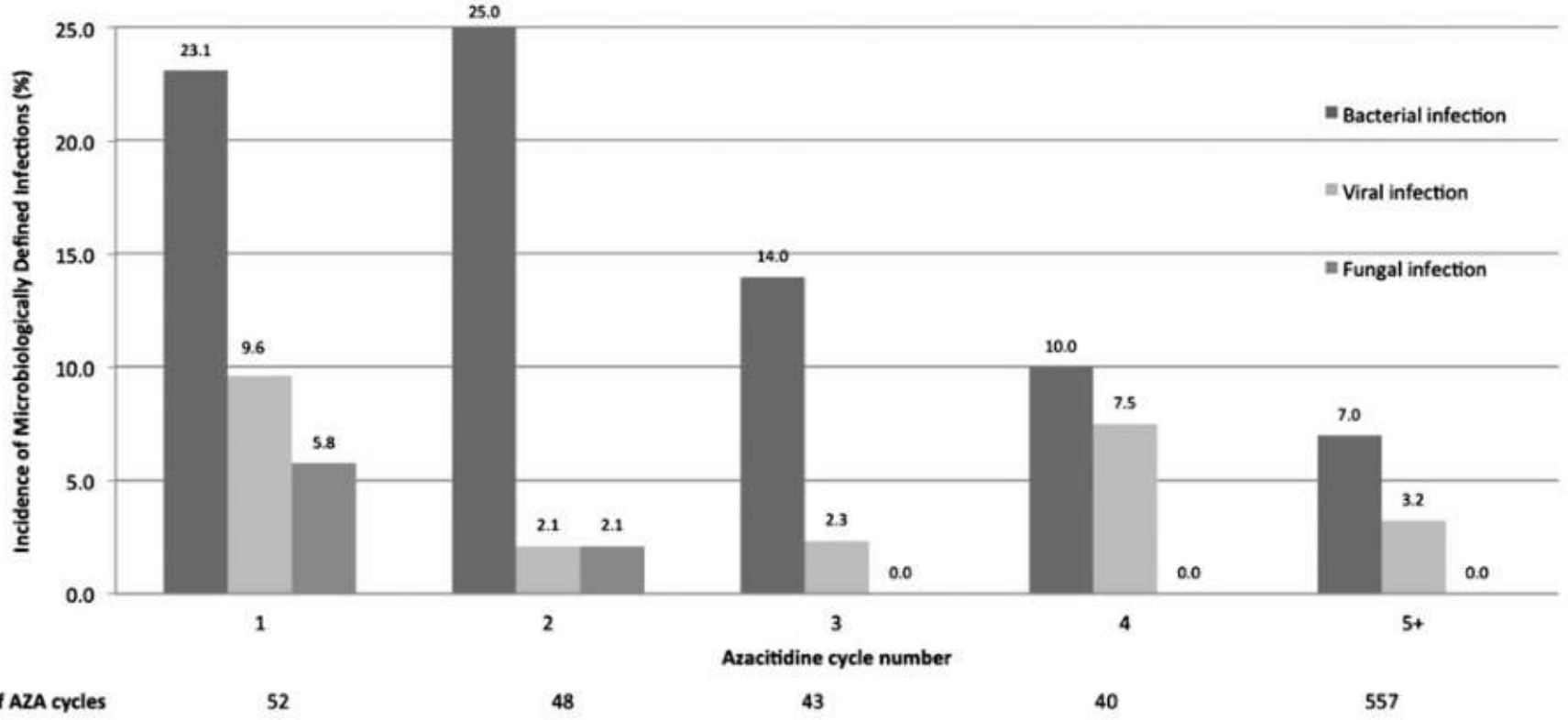
- **1.siklus öncesi**

  neu sayısı, plt sayısı, kötü sitogenetik olanlara dikkat!!

- Her siklus öncesi değerlendirme tekrar edilmeli.

Merkel D, Am j hematol 2013

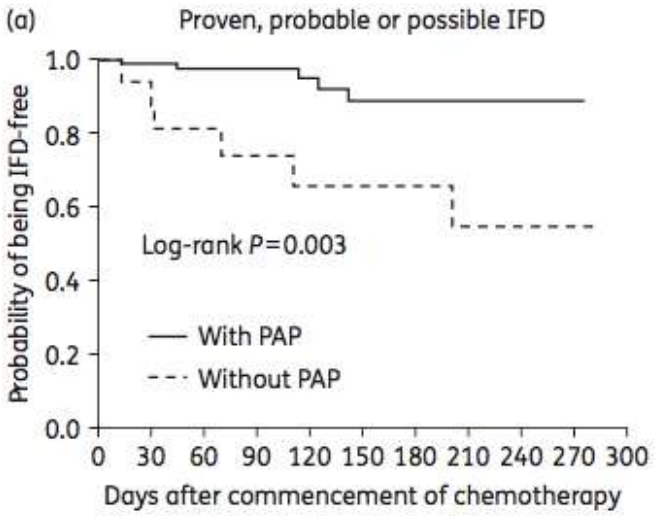
MDS'de fungal infeksiyon riski
-hipometile edici tedaviler-



Pomares H, Mycoses 2016

ALL'de fungal infeksiyon riski

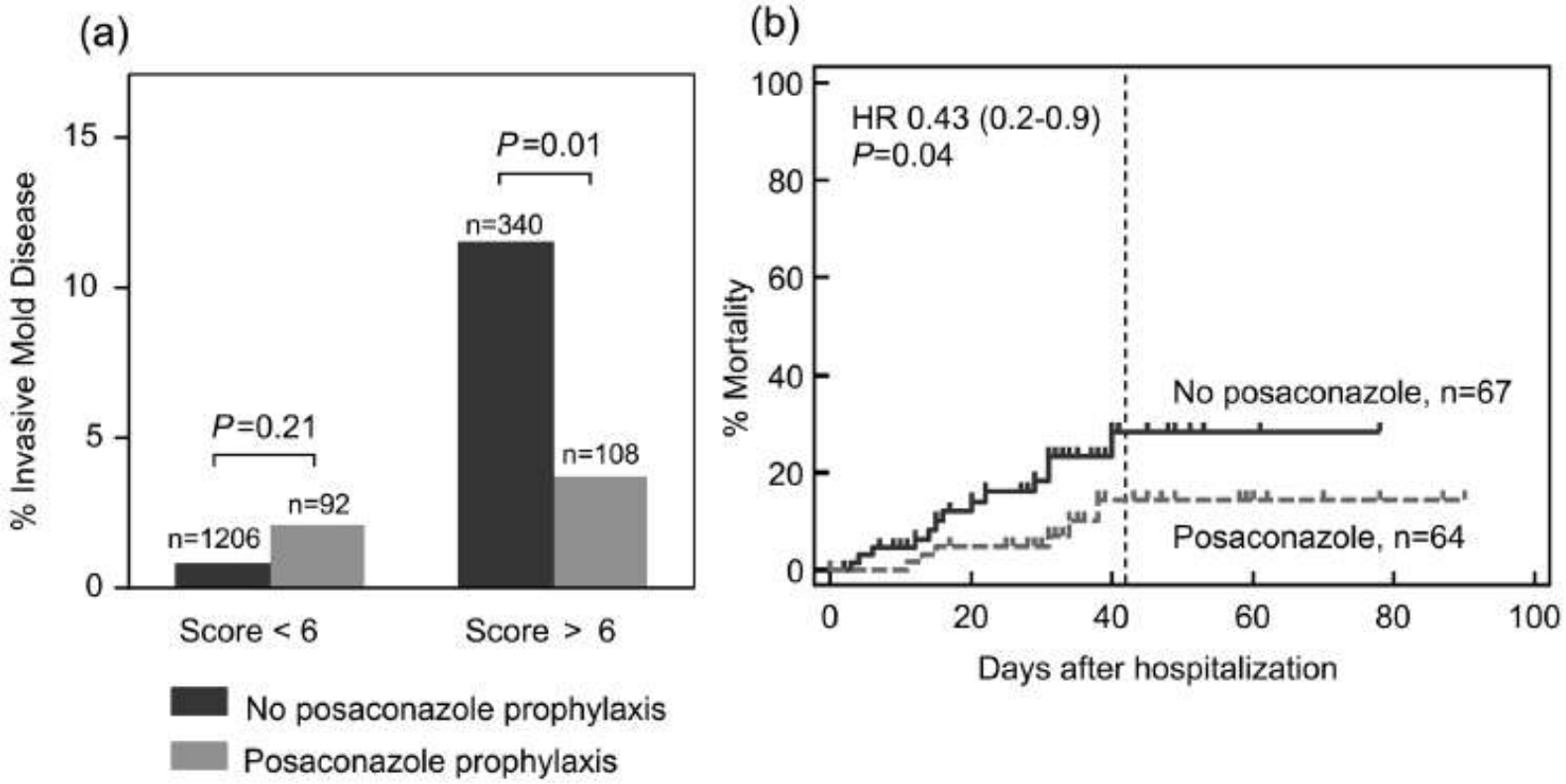
- İleri yaş
- Yüksek steroid kullanımı
- Relaps/refrakter olma riski artırır
- İndüksiyon sonrasına dikkat!!



Doan T, J Antimicrob 2016

Hematolojik malignite hastalarında invaziv küf mantarları riskini belirlemek için skorlama

Nötropeni, malignite durumu, lenfopeni, lenfosit disfonksiyonu, fungal inf.öyküsü



Stanzani, I Plos ONE 2013

Posaconazole vs. voriconazole in the prevention of invasive fungal diseases in patients with haematological malignancies: A retrospective study

L. Tang [a,b], X.-F. Yang [a,b], M. Qiao [a,b], L. Zhang [a,b], X.-W. Tang [a,b], H.-Y. Qiu [a,b], D.-P. Wu [a,b], A.-N. Sun [a,b,*]

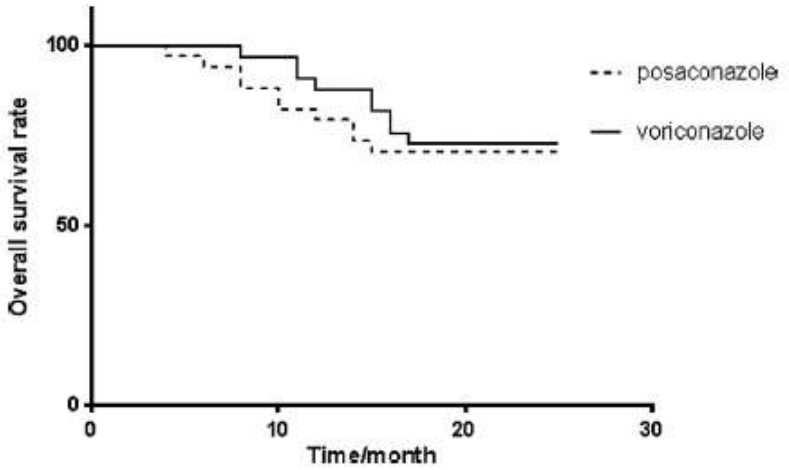


Figure 1 Kaplan–Meier analysis of overall survival between the posaconazole group and the voriconazole group ($P = 0.688$).

N=81

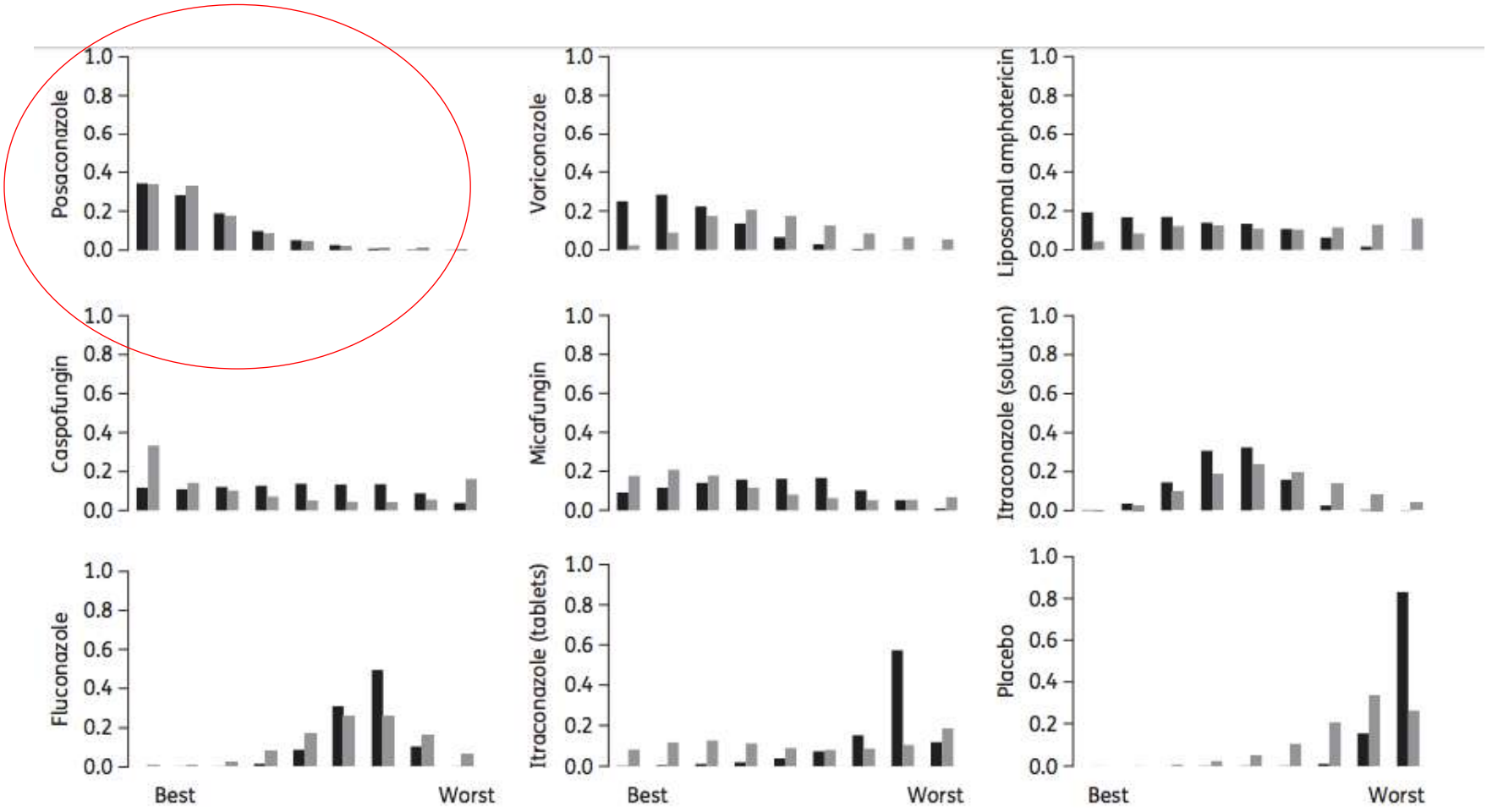
N=83

Yan etki ve ilacı kesmek:
Vorikonazol grubunda daha fazla
P=0,021

ABD MD Anderson'dan 2017 de benzer bir çalışma da aynı şekilde yan etki
Vori % 6 vs Posa % 1, p=0,03.

J Mycol Med. 2018 Jun;28(2):379-383.
Int J Antimicr Agents. 2017 Sep;50(3):384-388.

Posakonazol IFI riskini ve tüm sebeplere bağlı mortaliteyi azaltır!!



Pechlivanoglu ,J antimicrob Chemo 2016

Ekonomik mi?

	Antifungal prophylactic agents		
	Posa	Itra	Fluco
Antifungal prophylaxis			
No. of patients	510	120	175
Total cost[a] (€)	591.513	4.416	1.820
Costs per patient (€)	1.160	37	10
Systemic antifungal treatment			
No. of patients	140	56	48
LF-AmB	91	27	24
Echinocandin	38	21	13
Mold-active azoles	11	8	11
Total cost[a] (€)	1612.830	472.559	359.579
Costs per patient (€)	11.520	8.439	7.491
Total cost antifungal agents (€)	2204.343	476.975	361.399
Overall cost of all antifungal agents per patient (€)	4.322	3.975	2.065
Success rate[b]	85.7%	78.3%	74.3%
Total cost antifungal agents (€) Monte Carlo simulation	570.536	810.858	510.089

Busca A ,Leuk Lymp 2017

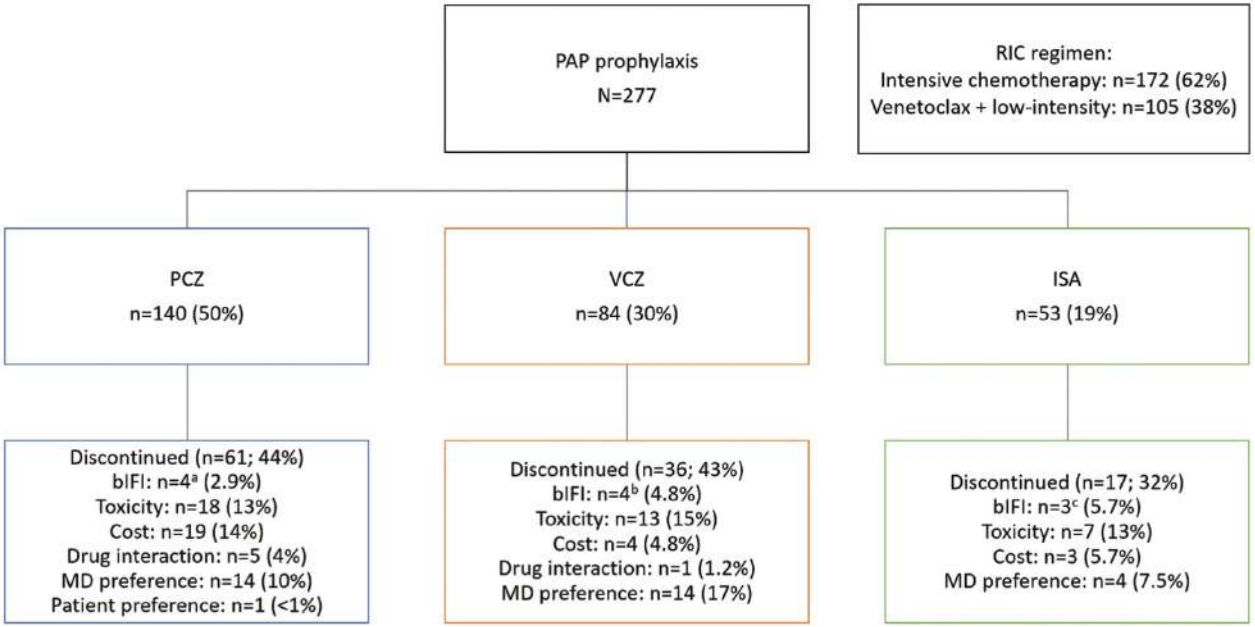
Clinical Infectious Diseases

MAJOR ARTICLE

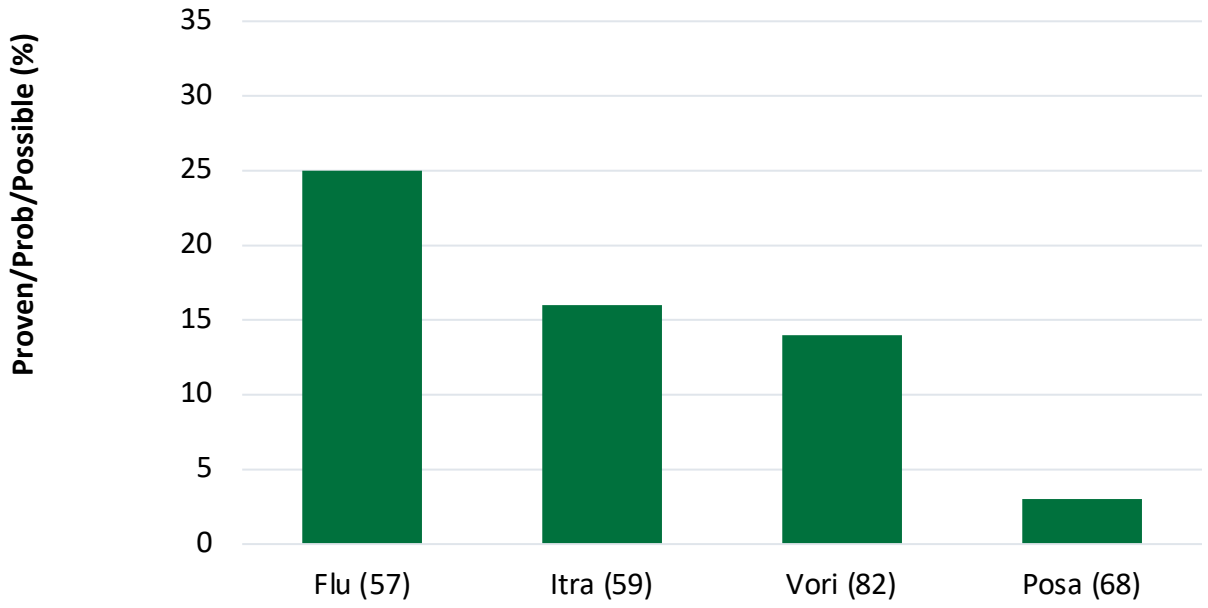
Comparison of Mold Active Triazoles as Primary Antifungal Prophylaxis in Patients With Newly Diagnosed Acute Myeloid Leukemia in the Era of Molecularly Targeted Therapies

Caitlin R. Rausch,[1] Adam J. DiPippo,[1] Ying Jiang,[2] Courtney D. DiNardo,[3] Tapan Kadia,[3] Abhishek Maiti,[3] Guillermo Montalban-Bravo,[3] Farhad Ravandi,[3] Dimitrios P. Kontoyiannis[2]

[1]Division of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [2]Department of Infectious Diseases, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; and [3]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, Texas, USA



‘Breakthrough’ infeksiyonlar



Anada-Rajah MR, *Haematologica* 2012

‘Breakthrough’ infeksiyonlar

- Primer posakonazol profilaksisi sırasında ‘breakthrough’ enfeksiyonlar %0-17.

Low CY, j Infect 2013
Aureberger J,J Antimicrob Chemo 2012
Winston DJ,BBMT 2011

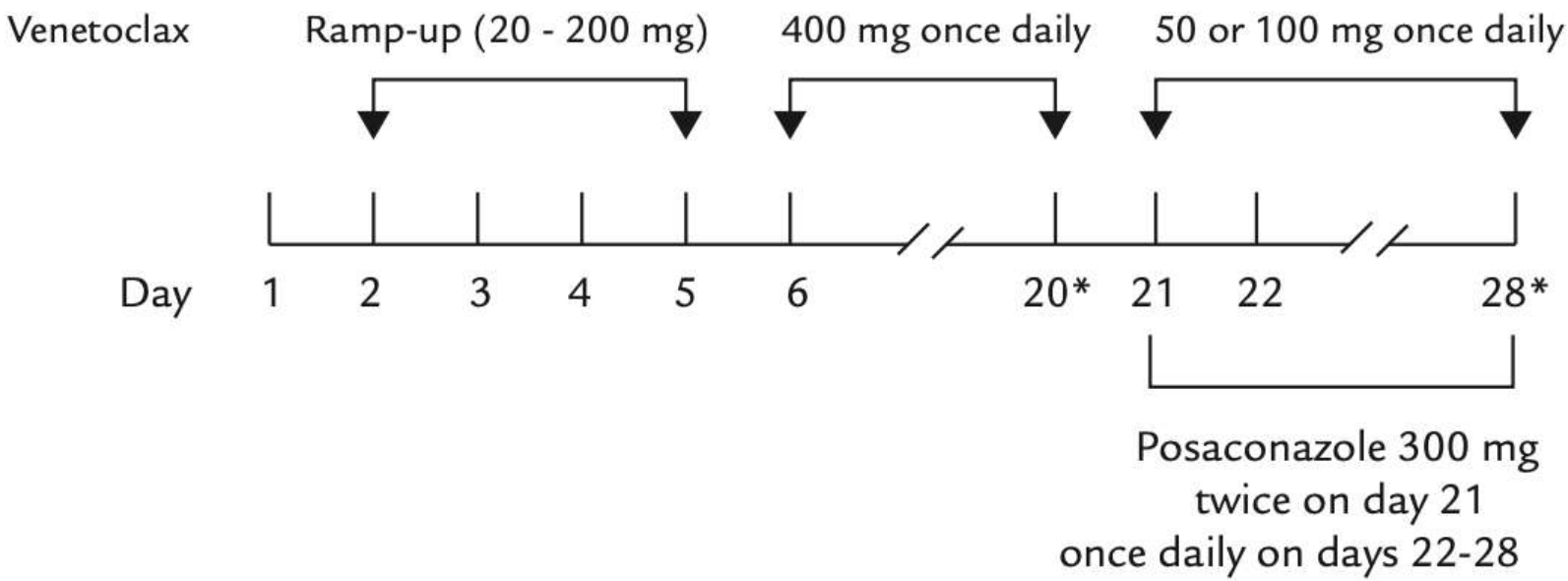
- Hastanın yaşı, indüksiyona yanıt,genetik ‘breakthrough ‘ enfeksiyon gelişme riskini artırır.

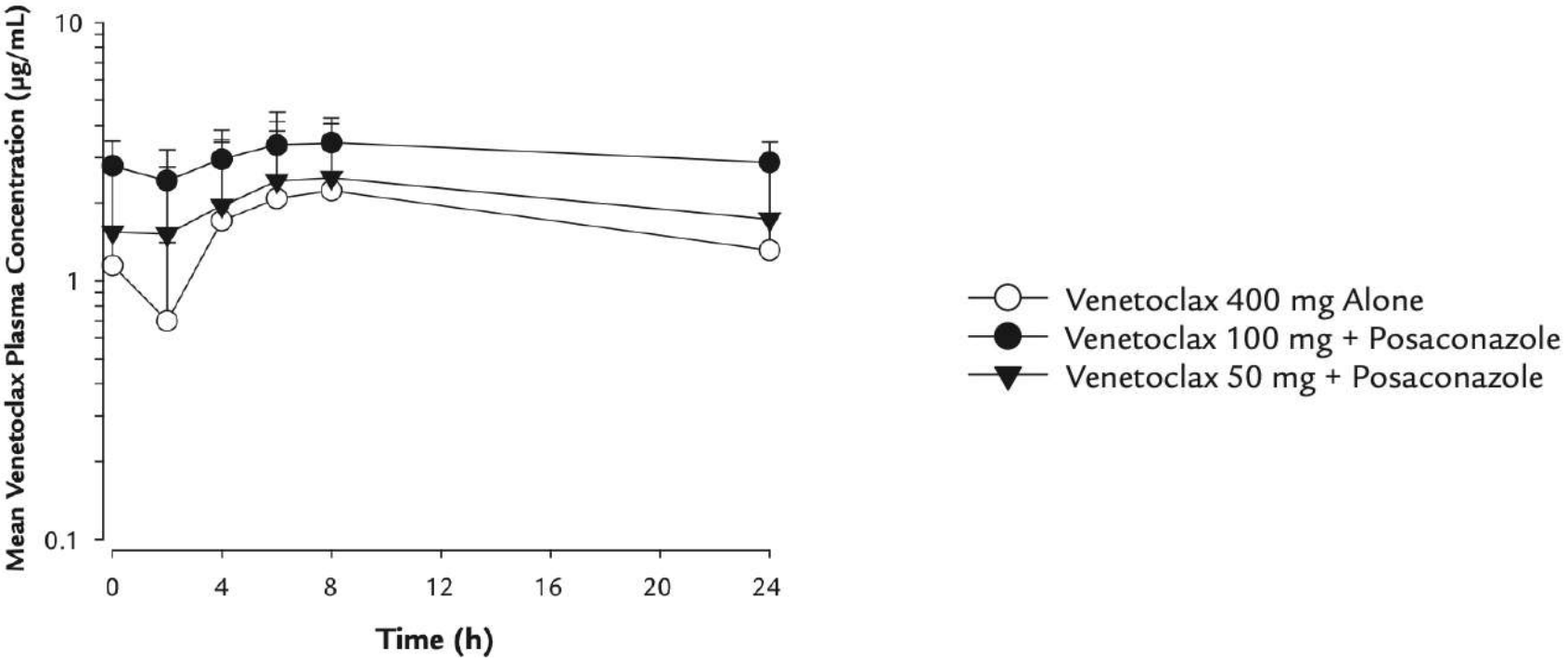
Michallet M,Mycoses 2011

Itraconazole	Potent CYP3A4 inhibitor, P-gp inhibitor and breast cancer resistance protein (BCRP) inhibitor.
Voriconazole	Inhibits CYP2C19, CYP2C9 and CYP3A4 enzymes.
Posaconazole	Potent CYP3A4 inhibitor.
Isavuconazole	Moderate CYP3A4/5 inhibitor, mild CYP2B6 inducer, mild P-gp inhibitor, mild inhibitor of organic cation transporter 2 (OCT2) and UGT.

	Enzymes	Transport proteins	QT prolongation
Acalabrutinib	3A4	P-gp, BCRP	
Bendamustine	1A2		
Bleomycin	Hydrolases		
Bortezomib	1A2, 3A4, 2C9		YES
Bosutinib	3A4		YES
Carfilzomib	Peptidases		YES
Cyclophosphamide	?		YES
Cyclosporine	3A4	P-gp, OATP	
Cisplatin	-		
Cytarabine	Cytidine deaminase		
Selinexor	3A4, UGT		
Sirolimus	3A4	P-gp	
tacrolimus	3A4		YES
Thalidomide	-		
All-transretinoic acid	3A4		YES
Arsenic trioxide	-		YES
Venetoclax	3A4		
Vinblastine	3A4		
Vincristine	3A4	P-gp	

Venetoklaks & Posakonazol




Mean Venetoclax Plasma Concentration (µg/mL)
10
1
0.1
0
4
8
12
16
20
24
Time (h)
Venetoclax 400 mg Alone
Venetoclax 100 mg + Posaconazole
Venetoclax 50 mg + Posaconazole

50 yaş erkek hasta

- Yeni tanı standart risk AML

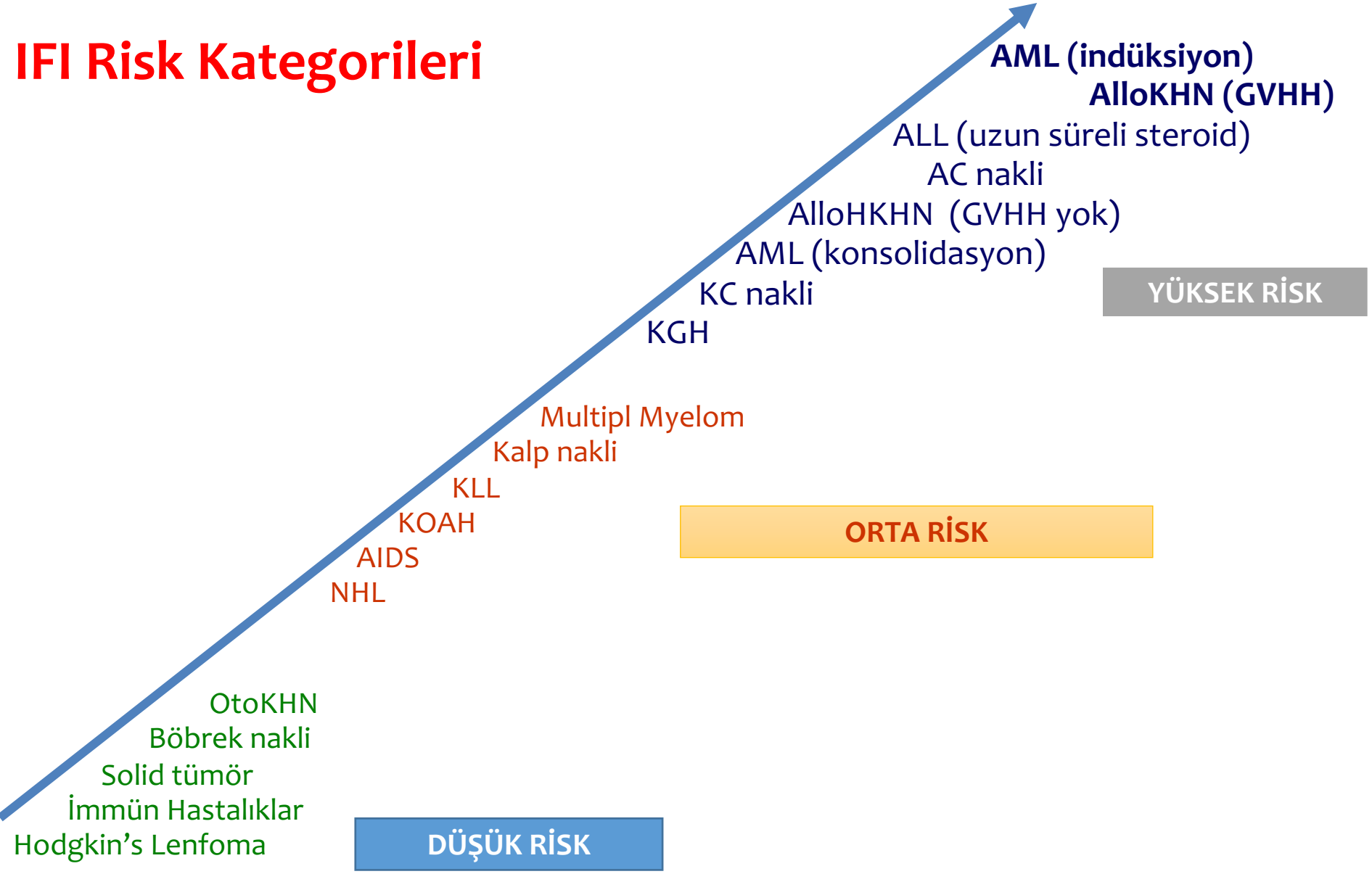
- ‘7+3’indüksiyon kemoterapisi aldı→posakonazol
- 1 konsolidasyon →flukonazol

- Özgeçmiş:KOAH

- 1.TR’da APKHN (haploidentik vericiden)

- +5. ay kronik GvHH

IFI Risk Kategorileri



Pagano et al, J Antimicrob Chemother, 2011
Herbrecht et al, Ann N Y Acad Sci. 2012

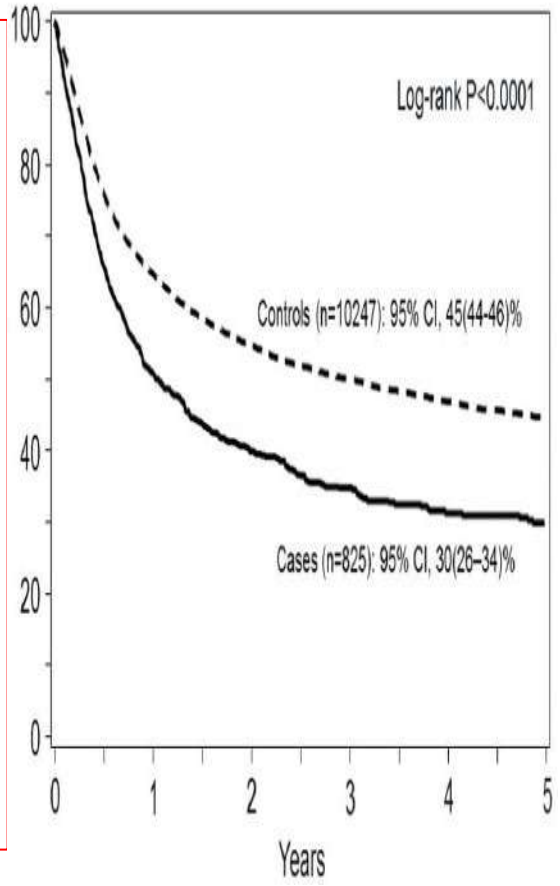
ALLOJENEİK KÖK HÜCRE NAKLİ ve IFI

CIBMTR verisi;

Nakil öncesi IFI(+) 825 vs 10247 IFI(-)

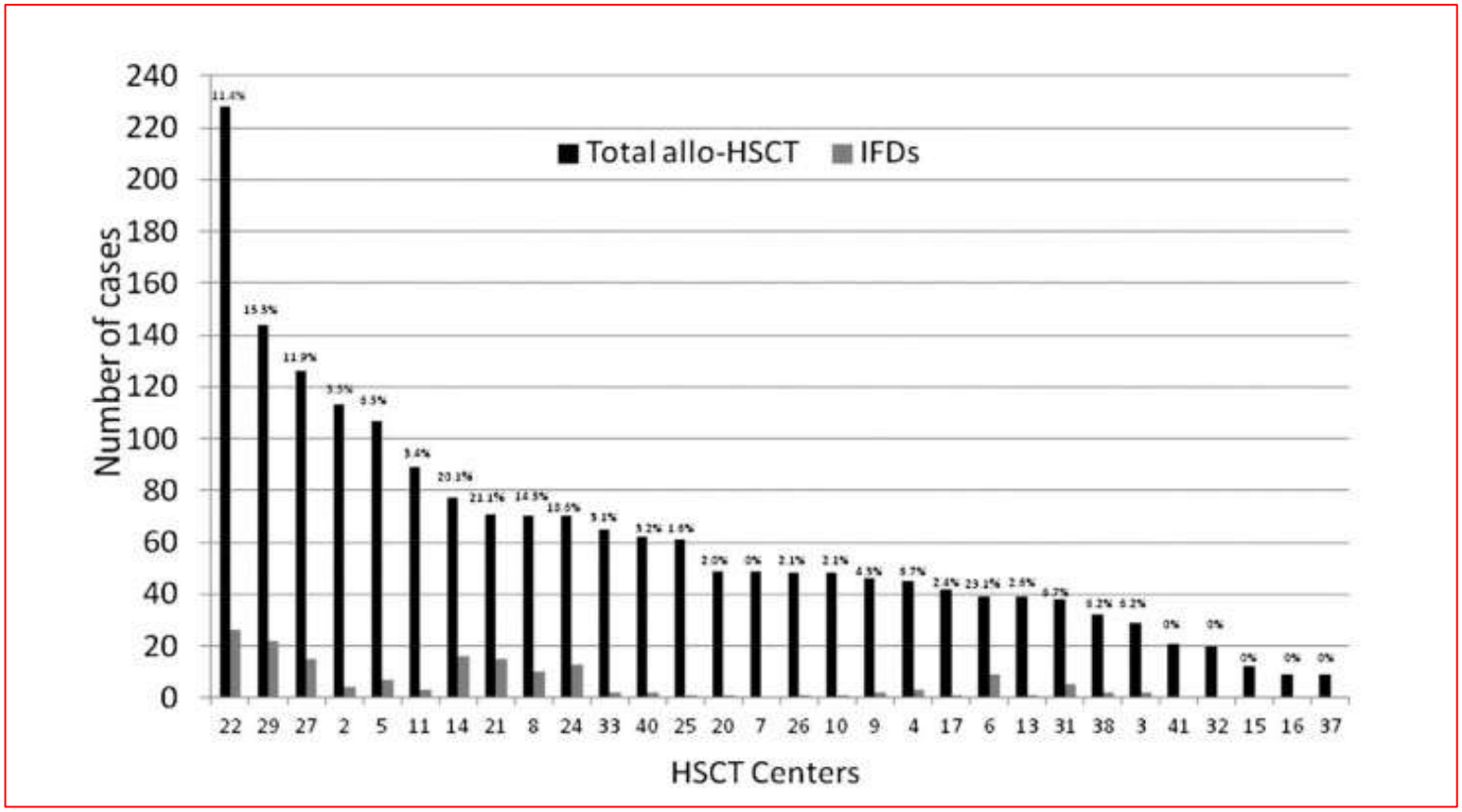
Progresyonsuz ve genel sağkalım IFI(+)lerde kısa

Nonrelaps mortalite yüksek ama relaps aynı.



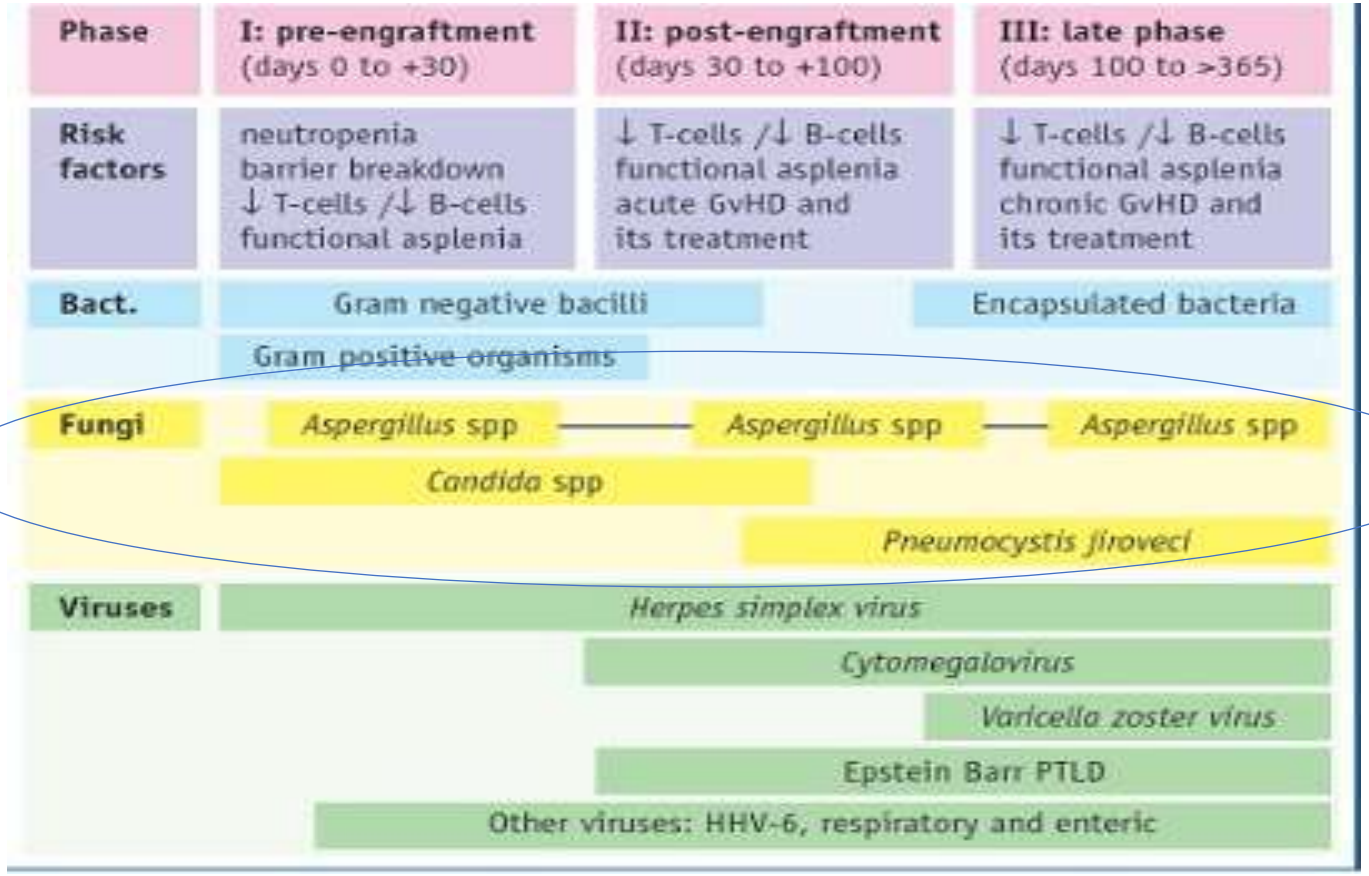
Maziarz RT,BMT 2017

Merkezlerin AHKHN sayısı
IFI riskini belirler!!



Girmenia C,BBMT 2014

Allojeneik nakil'de fungal infeksiyon riski

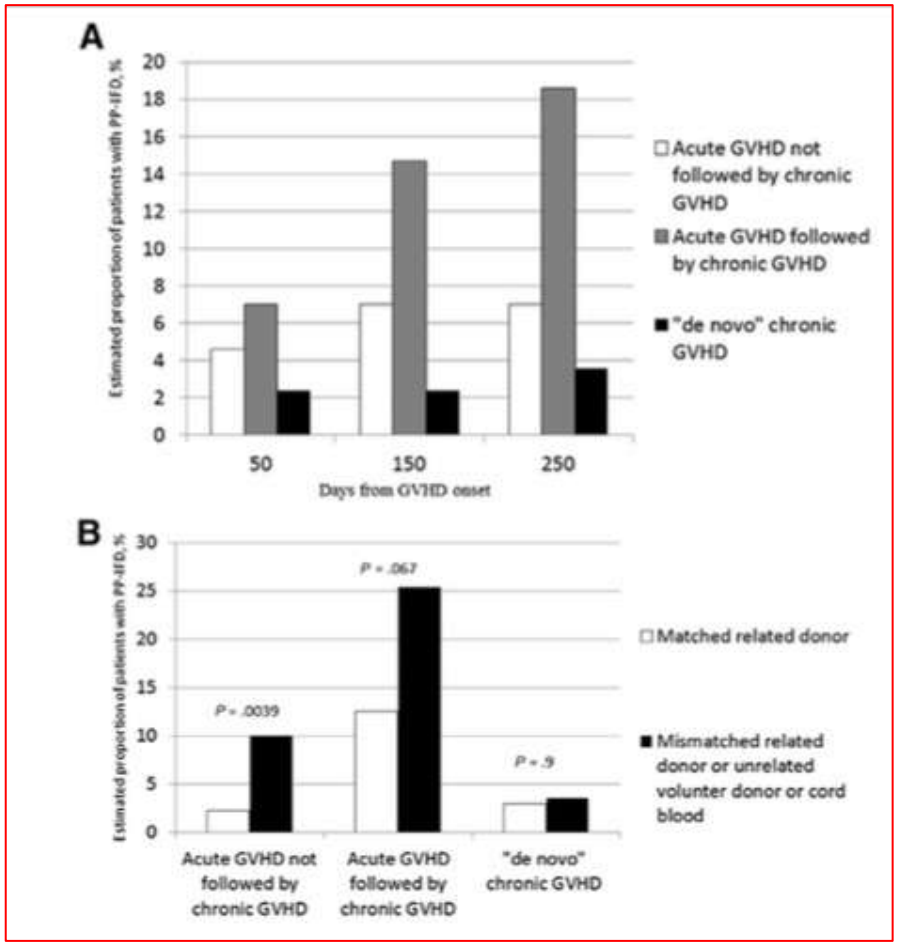


AHKN IFI riskini belirleyen faktörler

NAKİL ÖNCESİ	NAKİL DÖNEMİ	NAKİL SONRASI
İleri yaş Tanı Hastalık durumu Demir yükü Genetik DM	IFI öyküsü EBMT skoru Kateter MUD/Kord/Haplo Kök hücre dozu ATG/alemtuzumab	Akut/kronik GVHH Steroid/infliksimab Nötropeni/lenfopeni CMV/parainfluenza Hipoalbuminemi YBÜye yatış

Pagano L,Blood Rev 2017

AHKN IFI riskini belirleyen faktörler



NAKİL SONRASI

Akut/kronik GVHH
Steroid/infliksimab
Nötropeni/lenfopeni
CMV/parainfluenza
Hipoalbuminemi
YBÜye yatış

Pagano L,Blood Rev 2017

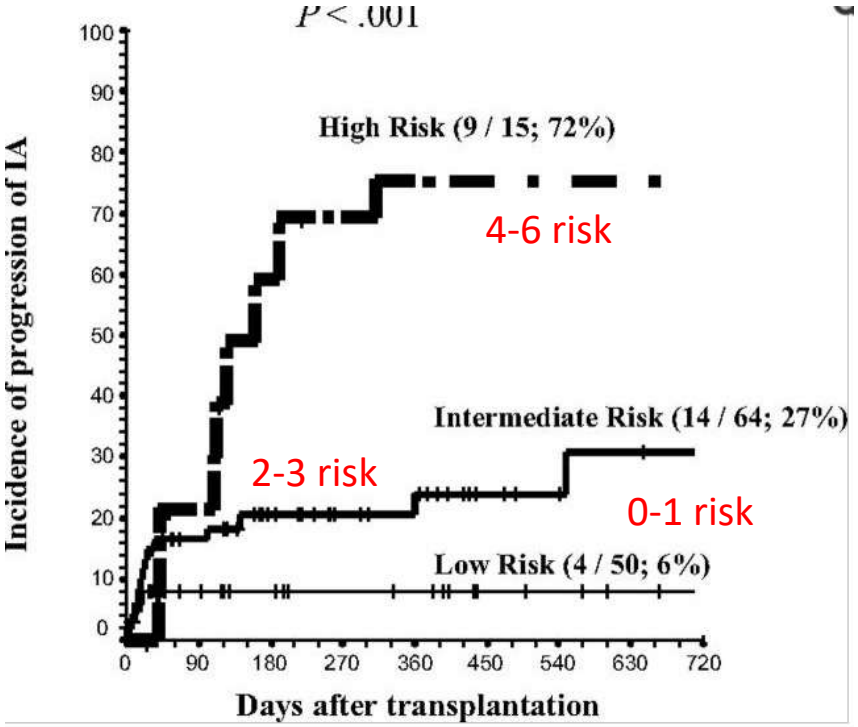
Kök hücre nakli sonrası kimde IA nüks etme olasılığı fazla?

Engraftman öncesi;

Uzamış nötropeni
Sistemik antifungal-nakil arası<6 hafta
Alttaki hastalık statusu
Hazırlık rejimi

Engrafman sonrası;

K.Iliği veya kordon kanı kullanılması
CMV infeksiyonu
Akut GVHH



Martino R,Blood 2006

Post-engrafman IFI riski

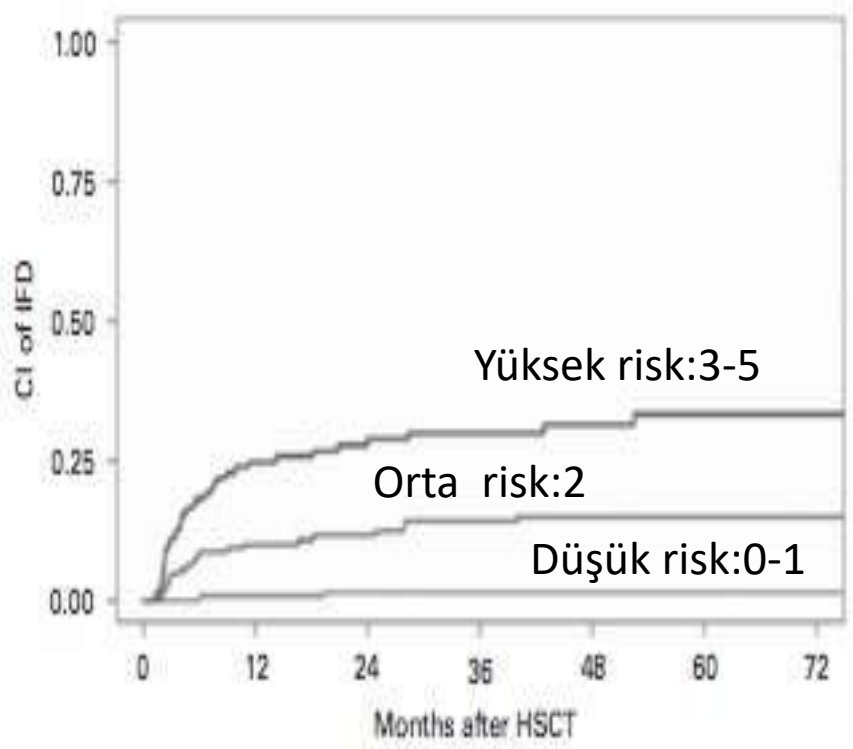
>40 yaş

Nötropeni>15 gün

Kronik GVHH

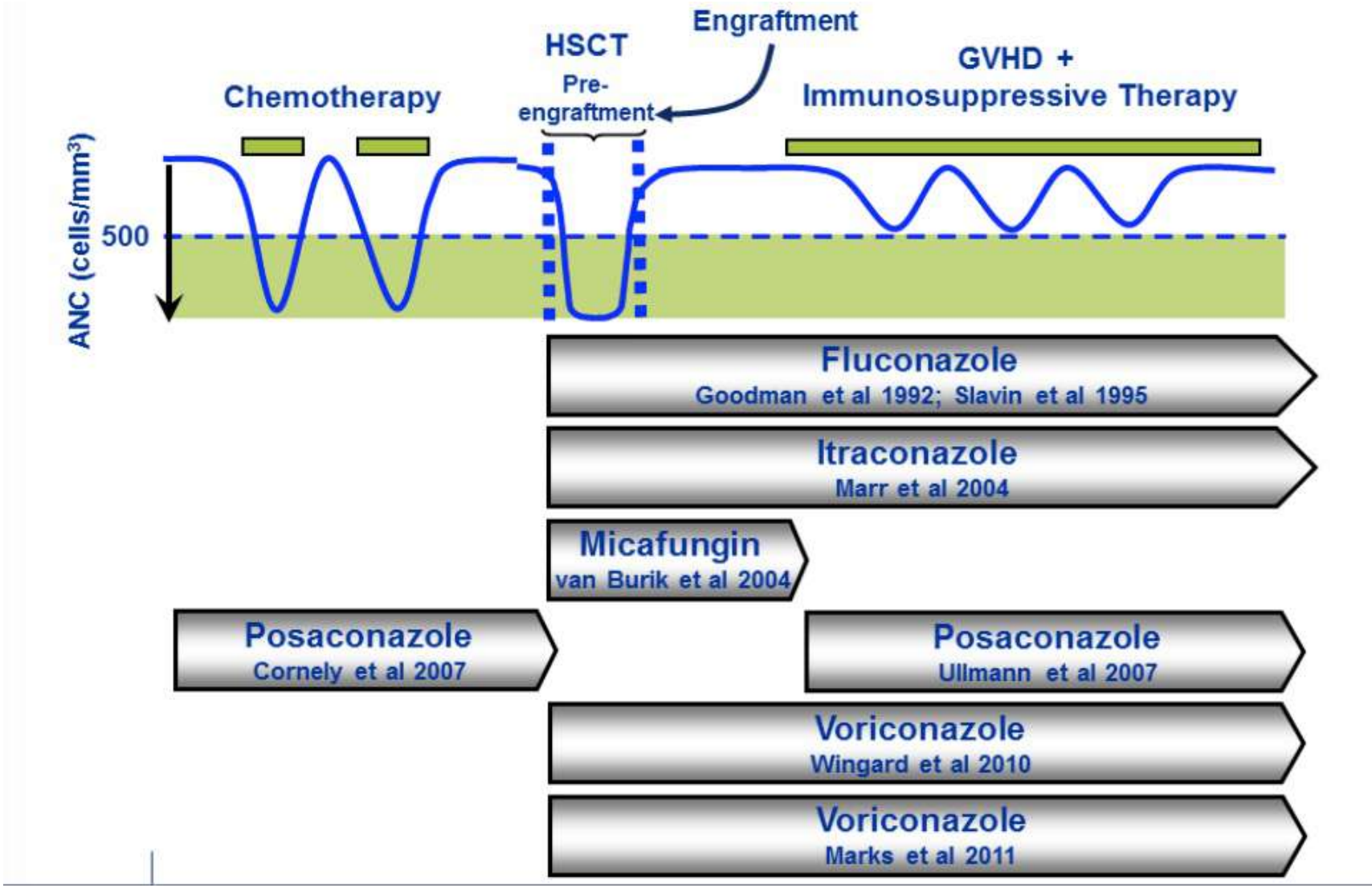
2.nakil

CMV enfeksiyonu

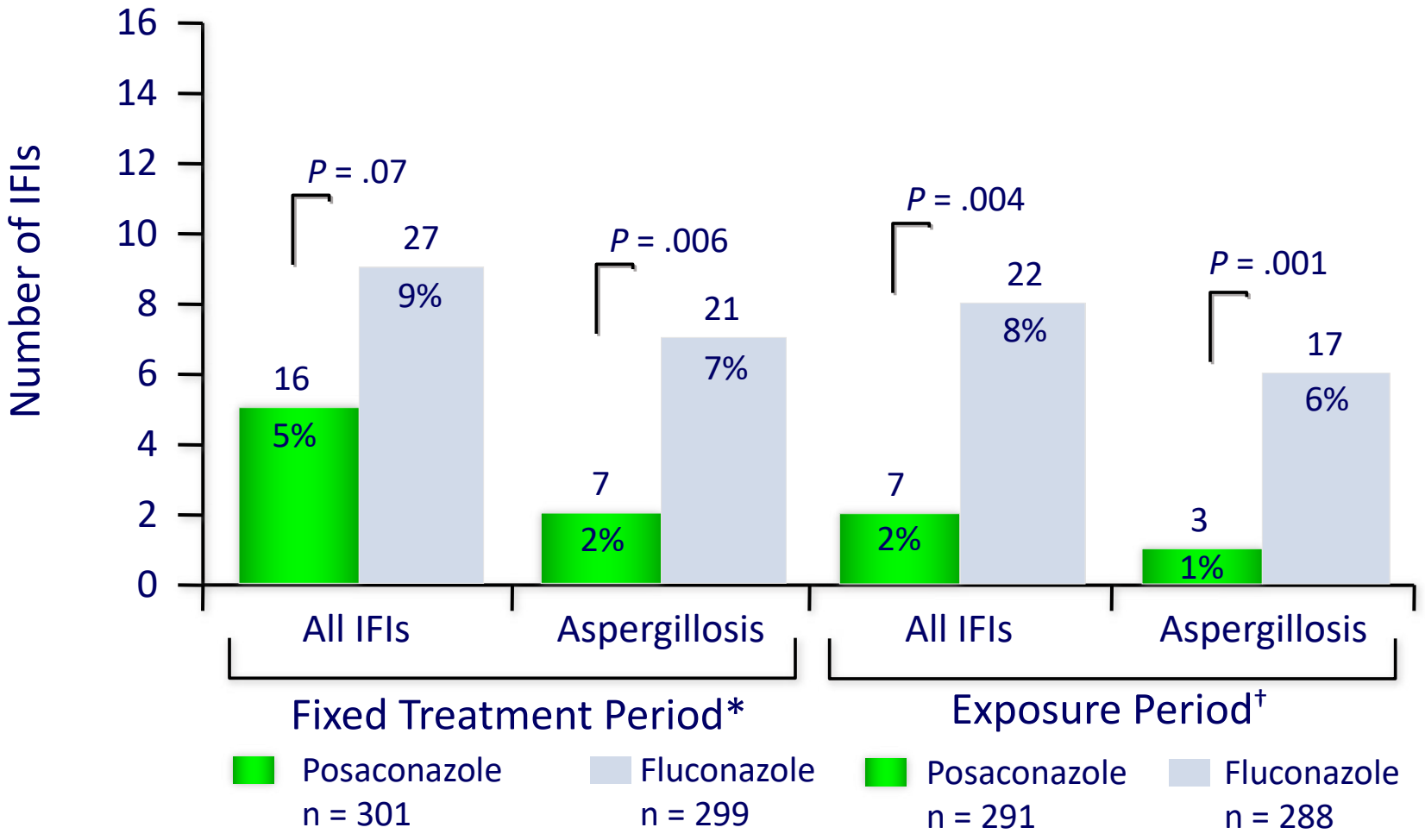


Montesinos p,BMT 2015

AHKN'de antifungal profilaksi



GVHD olan Allo-KHN hastalarında posakonazol profilaksisi



Ullman et al. NEJM 2007

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Andrew J. Ullmann, M.D., Jeffrey H. Lipton, M.D., David H. Vesole, M.D., Ph.D., Pranatharthi Chandrasekar, M.D., Amelia Langston, M.D., Stefano R. Tarantolo, M.D., Hildegard Greinix, M.D., Wellington Morais de Azevedo, M.D., Ph.D., Vijay Reddy, M.D., Navdeep Boparai, M.S., Lisa Pedicone, Ph.D., Hernando Patino, M.D., and Simon Durrant, M.D.*

Event	Posaconazole Group (N=301)	Fluconazole Group (N=299)
	no. (%)	
Deaths		
All causes		
During the observation period	76 (25)	84 (28)
During the fixed treatment period	58 (19)	59 (20)
During the exposure period†	22 (8)	24 (8)
Cause of death		
Adverse event	39 (13)§	37 (12)
Invasive fungal infection		
Complications of infection‡	4 (1)	12 (4)
Proven or probable infection§	2 (1)	11 (4)
Possible infection	2 (1)	1 (<1)
Progression of underlying disease or GVHD	31 (10)	33 (11)
Other	2 (1)	2 (1)

Postengraftman

Antifungal agent	High risk GvHD
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	A-I[a,b]
Itraconazole oral solution 2.5 mg/kg q12h	B-I[b]
Voriconazole 200 mg q12h	B-I[b]
Micafungin 50 mg q24h	C-II
Caspofungin and anidulafungin	no data
Liposomal amphotericin B	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h	no data
Fluconazole 400 mg q24h	A-III against

Maertens J,JAC 2018

AHKHN rehber önerileri

ACUTE LEUKEMIA WITH PROLONGED NEUTROPENIA	ESCMID°	ECIL-5"	IDSA^
Fluconazole	-	B I	-
Itraconazole	D II	B I	Strong Recommendation/Moderate-QEv
Voriconazole	C II	B II	Strong Recommendation/Moderate-QEv
Posaconazole	A I	A I	Strong Recommendation/High-QEv
L-AmB/ABLC	C II	C II	-
Autologous HSCT			
Any antifungal agent	D III	-	-
Allogeneic HSCT until engraftment			
Fluconazole	-	A I[§]	-
Itraconazole	D I	B I	Strong Recommendation/Moderate-QEv
Voriconazole	C I	B I	Strong Recommendation/Moderate-QEv
Posaconazole	B II	B II	Strong Recommendation/High-QEv
Micafungin	C I	B I/C I[#]	-
Allogeneic HSCT with GVHD			
Fluconazole	-	A I/A III against*	
Itraconazole	C II	B I	Strong Recommendation/Moderate-QEv
Voriconazole	C II	B I	Strong Recommendation/Moderate-QEv
Posaconazole	A I	A I	Strong Recommendation/High-QEv
Micafungin	C III	C II	Weak Recommendation/Low-QEv

Alessandro Buscaa and Livio Paganob. Expert Rev Anti Infect Ther. 2018 Jul;16(7):531-542

Azol ilaç etkileşimlerine dikkat!!

	CYP3A4		CYP2C9		CYP2C19		P-gp	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Fluconazole	++	0	++	0	+	+	0	0
Itraconazole	+++	+++	+	0	0	0	+++	++
Voriconazole	++/+++	+	+	0	++	+++	0	0
Posaconazole	++	0	0	0	0	0	++	+
Isavuconazole	+/++	++	0	0	0	0	+	0

Girmenia G,Exp Op Drug Safety 2016

Azol ilaç etkileşimlerine dikkat!!

Drug	Co-administration with CYP3A4 substrates	Co-administration with strong CYP3A4 inhibitors (itraconazole and voriconazole)	Co-administration with moderate CYP3A4 inhibitors (posaconazole and fluconazole)	Co-administration with weak CYP3A4 inhibitors (isavuconazole)
Cyclosporine	Cyclosporine may increase the level of itraconazole. P-gp also involved	CYP inhibitors increase the level and the effect. P-pg also involved. TDM based dosing. Consider early dose reduction (50%)	CYP inhibitors increase the level and the effect. TDM based dosing. No empiric reduction while waiting for TDM required	CYP inhibitors increase the level and the effect. TDM based dosing. No empiric reduction while waiting for TDM required
Tacrolimus	Cyclosporine may increase the level of itraconazole. P-gp also involved	CYP inhibitors increase the level and the effect. P-pg also involved. TDM based dosing. Consider early dose reduction	CYP inhibitors increase the level and the effect. TDM based dosing. No empiric reduction while waiting for TDM required	CYP inhibitors increase the level and the effect.TDM based dosing. No empiric reduction while waiting for TDM required
Sirolimus	Cyclosporine may increase the level of itraconazole.	CYP inhibitors increase the level and the effect. P-pg also involved. Avoid coadministration	CYP inhibitors increase the level and the effect. TDM based dosing. Consider early dose reduction	CYP inhibitors increase the level and the effect. TDM based dosing.
Mychophenolate mofetil	No clinically relevant effect	No clinically relevant effect	No clinically relevant effect	No clinically relevant effect
Steroids	Steroids may decrease the levels of itraconazole	CYP inhibitors increase the level and the effect of steroids. P-pg also involved. Clinical evaluation	CYP inhibitors increase the level and the effect of steroids. Clinical evaluation	No clinically relevant effect

Girmenia G,Exp Op Drug Safety 2016

Rehberlere uyum???

Guideline	Number of patients
Patients who received prophylaxis (%)	68/90 (75.50)
Correct dosage (%)	60/68 (88.20)
Leukopenic when starting posaconazole (%)	23/68 (33.82)
Aspergillus antigen measured twice weekly (%)	53/68 (77.95)
Concomitant therapy with a PPI* (%)	61/68 (89.70)
Documented interval between posaconazole and PPI* (%)	7/68 (10.30)
Patients continuing posaconazole until regeneration/discharge (%)	30/68 (44.10)
Posaconazole administered for longer than duration of leukopenia (%)	21/30 (70.00)
Posaconazole administered for shorter than the duration of leukopenia (%)	9/30 (30.00)

Berking S, Mycoses 2017

Teşekkürler