WAYNE STATE UNIVERSITY
SCHOOL OF MEDICINE

Prophylaxis Limitations: Challenges in the Management of Invasive Aspergillosis

Pranatharthi H. Chandrasekar, MD
Professor, Department of Medicine
Wayne State University School of Medicine
Karmanos Cancer Institute

Case Study: Patient Profile

- 55-year-old woman with myelodysplastic syndrome
- Developed GVHD of the skin and GI tract after matched allogeneic SCT
- Medications
  - Prednisone (20 mg/day) for past 3 months
  - Infliximab for refractory GVHD
  - Voriconazole (200 mg po bid) for the past 3 months as prophylaxis

GVHD = graft-versus-host disease; GI = gastrointestinal; SCT = stem cell transplant; po = by mouth; bid = twice daily.

Case Study: Physical Examination and Diagnostics

- Patient presents with temperature 100° Farenheit, cough, and shortness of breath
- CT chest showed nodular infiltrate in left lung
- Labs
  - WBC 5000 (80% PMN)/mm^3
  - Platelets 20000 mm^3
  - Hemoglobin 8 gm/dL
  - BAL: Asp. GM 5.1
  - BAL culture negative

Management?

CT = computed tomography; WBC = white blood cell; PMN = polymorphonuclear; BAL = bronchoalveolar lavage; GM = galactomannan.

What type of IA prophylaxis therapy do you initiate for high-risk patients?

a. Fluconazole
b. Voriconazole
c. Posaconazole
d. Caspofungin
e. None

IFI Prevention Practices

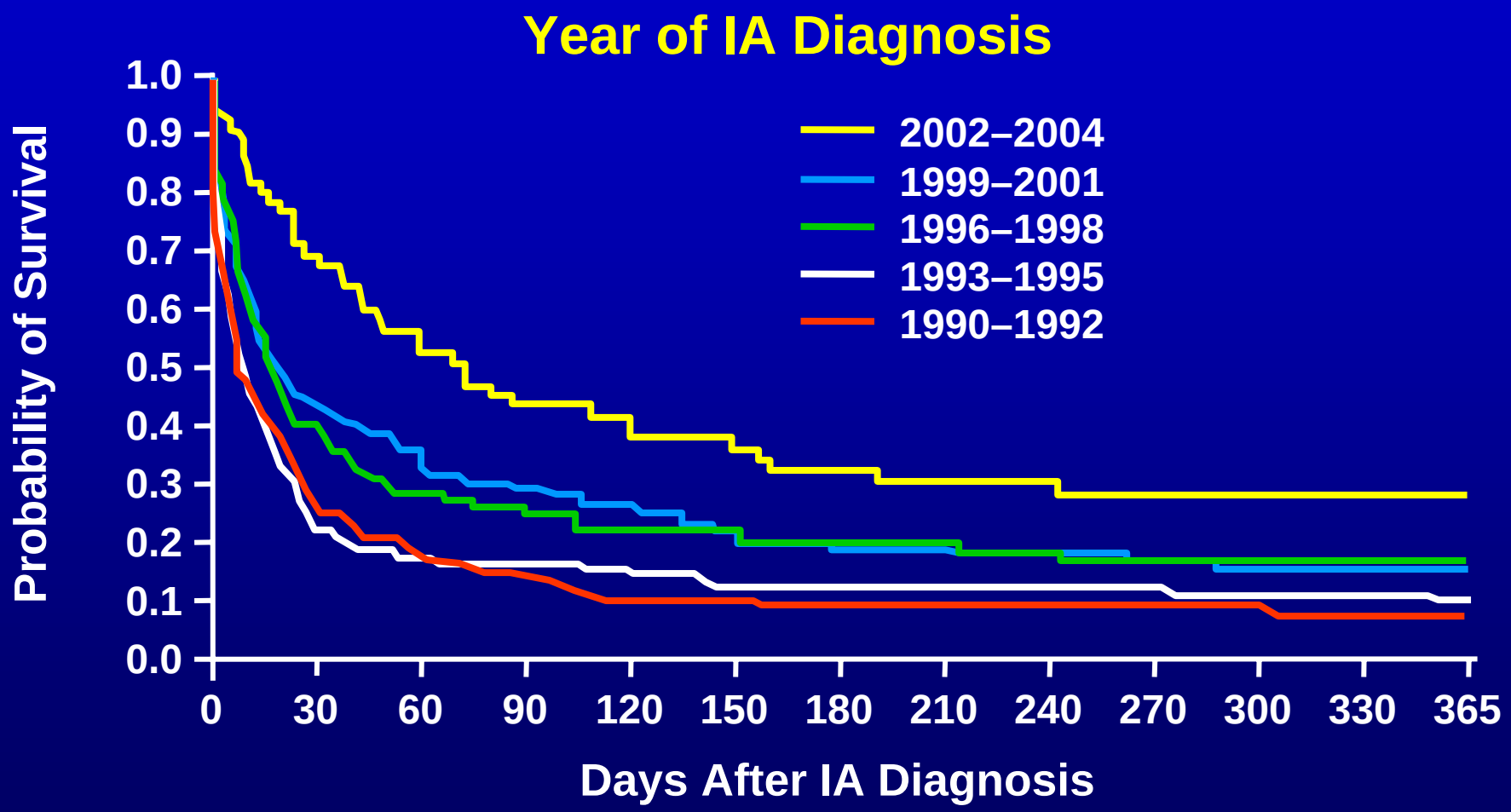
- Avoidance of potted plants and contact with soil
- Hand washing, masks (questionable)
- Water: drinking/showering
- Vascular access care
- HEPA filtration
- Reduced duration of neutropenia
- Reduced immunosuppression
- Chemoprophylaxis

IFI = invasive fungal infection; HEPA = high efficiency particulate air.

Antifungal Agents: FDA-Approved Indications for IA

Voriconazole	**Treatment** of IA
Posaconazole	**Prophylaxis** of IA in immunocompromised patients
Itraconazole	**Treatment** of pulmonary and extrapulmonary aspergillosis (*immunocompromised patients or non-immunocompromised patients intolerant of or refractory to AmB)*
Caspofungin	**Treatment** of IA (*patients refractory to or intolerant of AmB and/or itraconazole)*
Micafungin	**None**
Anidulafungin	**None**
AmB	**Treatment** of Aspergillus infections (*patients refractory to or contraindicated for AmB deoxycholate)*

Improvement in Clinical Outcomes for IA



Upton A et al. *Clin Infect Dis*. 2007;44:531.

Improvement in Clinical Outcomes for IA: Rationale

- Higher index of suspicion
- Earlier diagnosis (CT, GM)
- More aggressive workup
- More effective drugs (voriconazole)
- Changes in transplant practice
  - non-myeloabl. Tx
  - PBSCT
  - Shorter duration of neutropenia

ITRACONAZOLE : SCT Prophylaxis

140 Patients

I : 200 mg q 12h x 2d IV;
200 mg sol q 12 (d + 1 to d + 100)
F: 400 mg IV/PO q 24h

180d Post-SCT	I (%)	F (%)	*P*
Proven IFI	9	25	.01
Fungal-death	9	18	.13
IA	4	12	.12
Mort			NS
GI Intolerance	24	9	.02

Winston DJ, *Ann Intern Med* 138: 705, 2003.

304 Patients

I : 7.5 mg/kg/d sol with condition. regimen

IFI

Intent to Treat	I ≡ F	
On Treatment	I < F	(*P* .03)
Inv. Mold	I < F	(*P* .03)
Inv. Cand	I ≡ F	

Hepatotoxicity / GI Intolerance
I : 36% ; F : 16%

Marr KA, *Blood* 103: 1527, 2004.

Voriconazole Prophylaxis : Allogeneic SCT ('03-'06)

Prospective, Randomized, Double Blind Trial (600 pts)

Duration d 0 → d + 100/+180

Serum GM twice wkly x 60d, 1-2 wkly until d +100

Both Arms Similar in:

- Patient, Disease type, Transpl. type, Engraft. rate
- Acute/Chr. GVHD, non-fungal inf, study withdrawal

IFI : 25 Proven/30 Prob/15 Presump/74 Possible

- Proven/Prob/Presumptive IFI : Similar in 2 arms
- 6 mos: V 6.6%, F 10.6%; 12 mos V 11.6%, F 13.1%.
- Aspergillus: V 7, F16 (P=.05); Candida 3 & 3, Zygo 2 & 3

Fungal Free Survival 6 mos V 78%, F 76%

Event free / Overall Survival similar

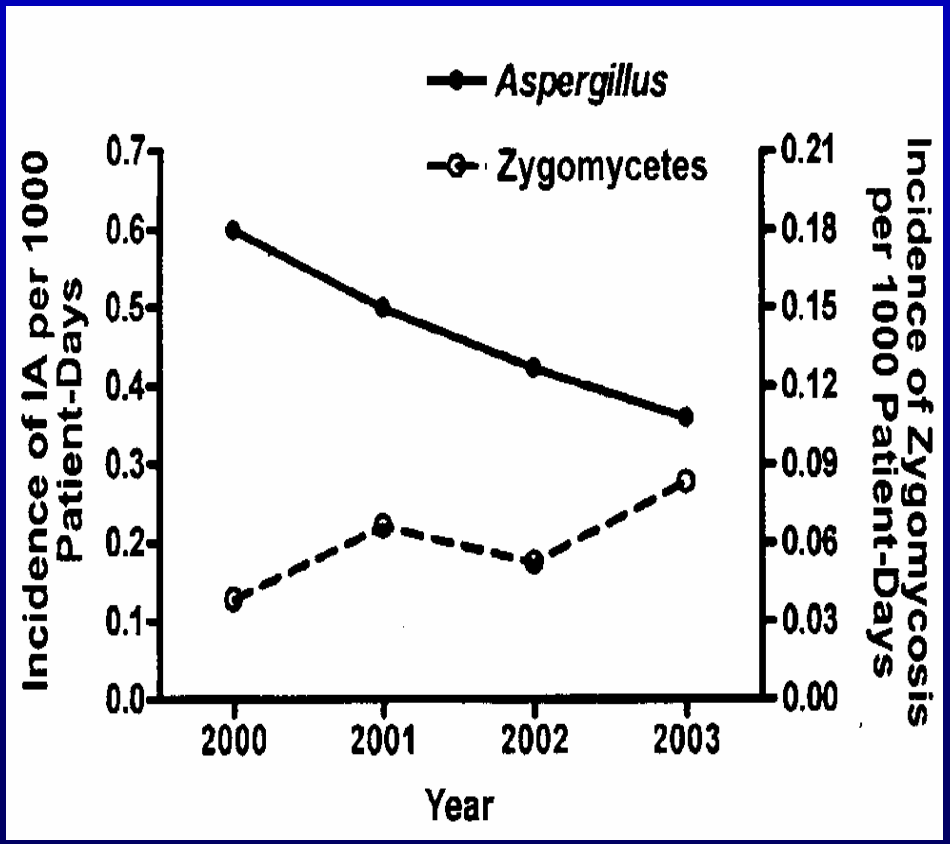
Concl : Efficacies of V and F are similar with close monitoring and early therapy

Wingard JR, Am Soc Hem 2007 (#163)

Zygomycosis Emergence : Voriconazole ('2002-2004) OBSERVATIONAL STUDY

27 PATIENTS (15 DEFINITE, 12 PROBABLE) [Ac leukemia; Allo SCT]
Voriconazole Prophy. 13/27 (48%)
(4 with Caspof)

	(27) Zygo (%)	(54) Inv Asp. (%)	*P*
VCZ Prophy. (≥5d)	48	11	.001
ITRA "	4	4	
Caspo "	15	6	
Hx Diab mellitus	3	15	.003
Malnutrition	70	49	.045



Kontoyiannis D. *J Infect Dis* 2005.

Antifungal Drugs : Drug Interactions

Azoles : CYP450 Interactions

Fluconazole	Inhibitor	3A4+++, 2C19++, 2C9++
Itraconazole	Inhibitor	3A4+++, 2C9+
	Inducer	3A4+++
Voriconazole	Inhibitor	2C19+++, 3A4++, 2C9++
	Inducer	2C19+++, 3A4+, 2C9+
Posaconazole	Inhibitor	3A4+++

Zaas AK, *J Inv Fungal Inf* 1:133, 2007

AZOLE INTERACTIONS: IMMUNOSUPPRESSIVE DRUGS

Via inhibition of hepatic CYP3A4

Cyclosporine/Tacrolimus

Signif ↑ drug plasma exposure

Recommend Starting Dose

with Vori Cyclosp ½; Tacro ⅓

with Posa Cyclosp ¾; Tacro ⅓

Sirolimus

with Vori. : 11 fold ↑ exposure

Dose red. By 90% → Satisfactory troughs

with Posa. ?

Monitoring Levels is important, including after discontinuation of Azole

Marty FM et al, *Biol Blood Marrow Transpl* 12:552, 2006

Posaconazole Prophylaxis : GVHD

- Randomized Double blind
- Fluconazole 400 mg QD vs posaconazole 200 mg TID
- Assessment at EOT + 7 days and 16 weeks
- Mean days on therapy
  - Fluconazole = 77
  - Posaconazole = 80
- Composite endpoint of proven/probable IFI, systemic antifungal, or death

	Posaconazole (n=301)	Fluconazole (n=299)
IFI total (*P*=0.07)	16(5.3%)	27(9.0%)
Proven/Probable IFI – *Candida* spp.	4(1%)	4 (1%)
Proven/Probable IFI – *Aspergillus* spp. (*P*=0.006)	7(2%)	21(7%)
Death – Proven/Probable IFI (*P*=0.01)	2(1%)	11(4%)

Ullmann AJ, et al. *N Engl J Med.* 2007;356:335-47.

Ullmann AJ, et al. *N Engl J Med.* 2007;356:335-47.

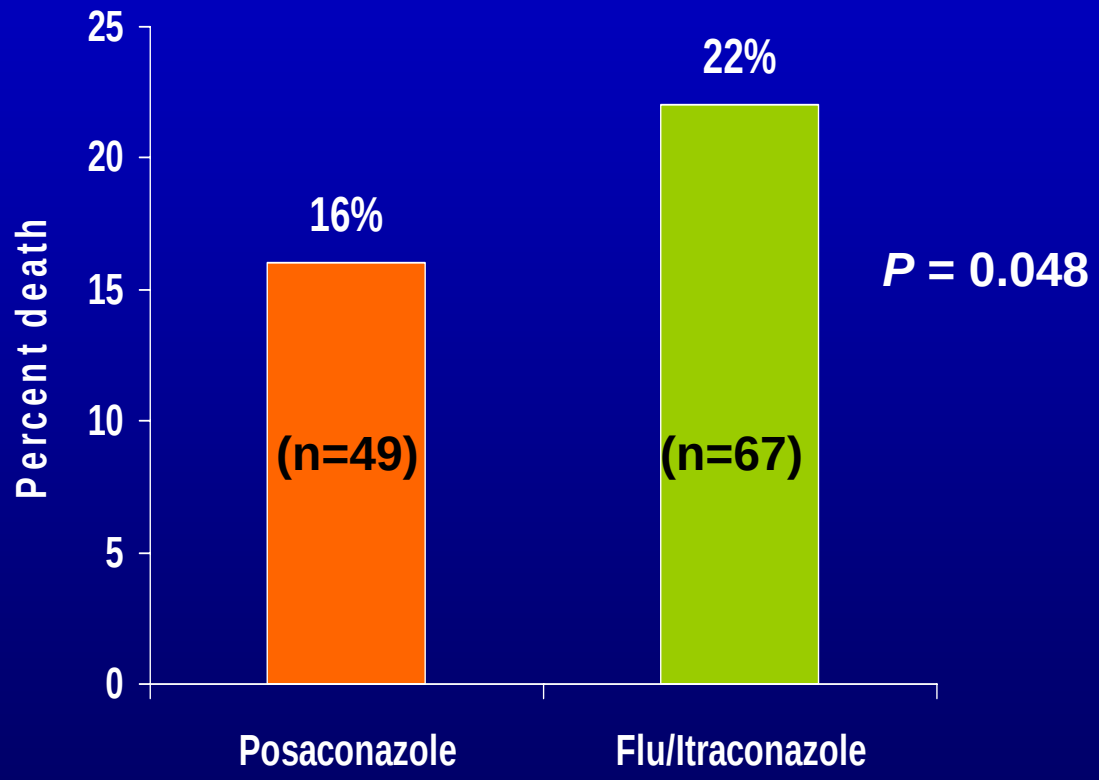
Posacon. Prophylaxis : Neutropenia (Heme Malignancy)

On Therapy + 7 days

	Posaconazole (n=304)	Flu/Itraconazole (n=298)
Proven/Probable IFI* (*P*<0.001)	7(2%)	25(8%)
Proven/Probable IFI – *Candida* spp.	2(1%)	3(1%)
Proven/Probable IFI – *Aspergillus* spp. (*P*=0.001)	2(1%)	20(7%)
Proven/probable IFI – Death	1(<1%)	2(1%)

*95%CI = -9.7%, -2.5%

100 days post randomization



Cornely OA, et al. *N Engl J Med.* 2007;356:348-59.

Daily Oral Schedule : SCT Recipient with GVHD

Difficulty with Posaconazole (oral)

	7am	*8	10	*12	2	*6	8	10pm
Tacrolimus (empty stom.)			x					x
Medrol		x					x	
Mycophenolate (empty stom.)	x				x			x
Posaconazole		x		x		x		

Magnesium not to be given with mycophenolate; 3-4 times/day

Others: Fluconazole, acyclovir, TMP/SMX, penicillin, Ativan, Compazine - prn

POSACONAZOLE PROPHYLAXIS : LIMITATIONS

- Oral Bioavailability –
  - Ability eat fatty meal
  - Selection bias / not so sick patients
  - Ø Serum concentrations
- Ac leukemia trial
  - Most ‘probable’ cases : Dx by Asp. Galactomannan only; if removed, Ø advant. with Posa.
- GVHD Trial
  - Posa : Baseline GM (+) : 21 (7%); IFI 2 (10%)
  - Flu : Baseline GM (+) : 30 (10%); IFI 7 (23%)
  - ? Pre emptive rather than prophylactic trial
  - Overall Mortality not reduced
  - Clin failure rates similar in both groups

Cornely OA, New Engl J Med 356: 348, 2007.
Ullmann AJ, New Engl J Med 356: 335, 2007.

Azoles: Monitoring Serum Levels

Voriconazole

Intra-/Inter-subject variability of levels

Genetic polymorphism of CYP enzymes

Concomitant drugs eg. HAART, Rifampin

Non linear kinetics

Serum level vs Efficacy

6 studies – no correlation

28 IFI pts : > 2.05 mg/L, Positive outcome

Serum level vs Toxicity

↑ LFT : 12% Vori. Recipients

10 clin. studies (> 1000 Patients) – correl. With LFT, visual abnorm

Recomm : Target level 2-6 mg/L

In whom? (Progr. Disease/?Adherence/?Toxicity/Drug Interact.)

Concern : Long term Voricon. Use → ↓ levels

Trifilio S et al, *BMT* 35:509, 2005. Vfend, Prescrib Inform, Nov 2006, Pfizer Pharm.
Smith J et al, AAC 50:1570, 2006.
Pascual A, Antimicrob Agents Chemother 51:137, 2007.

ANTIFUNGAL DRUGS : MONITORING SERUM LEVELS

Posaconazole

Interpatient variability

Salvage therapy of Inv Asperg.

Average Plasma conc (μg/mL)		
	0.134	24% response
	0.4 - 0.7	50% resp.
	1.25	75% resp.

FDA-Product inform

'lower conc increases risk of failure'

EU – Product inform (for Inv. Asp)

AUC/MIC 200 → positive clin outcome

Noxafil, Prescr Inform, Oct 2006(USA), Schering Corp; Noxafil, Europ Prescr Inform, Mar 2007. Sch-Plough, Europe; Walsh TJ et al, Clin Infect Dis 44:2, 2007.

AZOLES : RESISTANCE

Early Reports	-	Itraconazole
Mechanism	-	14 alpha sterol demethylase
		CYP51A gene (amino acid substitution)
Recent		Resist. To Itra./Vori./Posa. (9 patients)
		5 Bkthru IA; 4 Primary IA (1 died)
		AML-3; CGD-3; hyper-IgE -1; COPD-1
		Am Acid substitution at codon 98
Innate Resistance		A.ustus; A. nidulans; A. terreus (polyene resist.)

Denning DW et al, *Antimicrob Agents Chemother* 41:1364, 1997
Verweij PE et al, *NEJM*, 356:1481, 2007.

Resistance in Aspergillus Fumigatus

A.fumigatus : a complex group

Three new sibling species identified, based on polyphasic taxonomy (micro/macro morphology, extrolite patterns, ß-tubulin, calmodulin sequence)

A. lentulus (relative resist to AmB, Vori, Caspof.)

A. fumigatiaffinis

A. novofumigatus

Balajee SA et al, Eukaryot Cell 4: 625, 2005
Hong S et al, Mycologia 97: 1316, 2005

Caspofungin: Prophylaxis (Heme Malignancy)

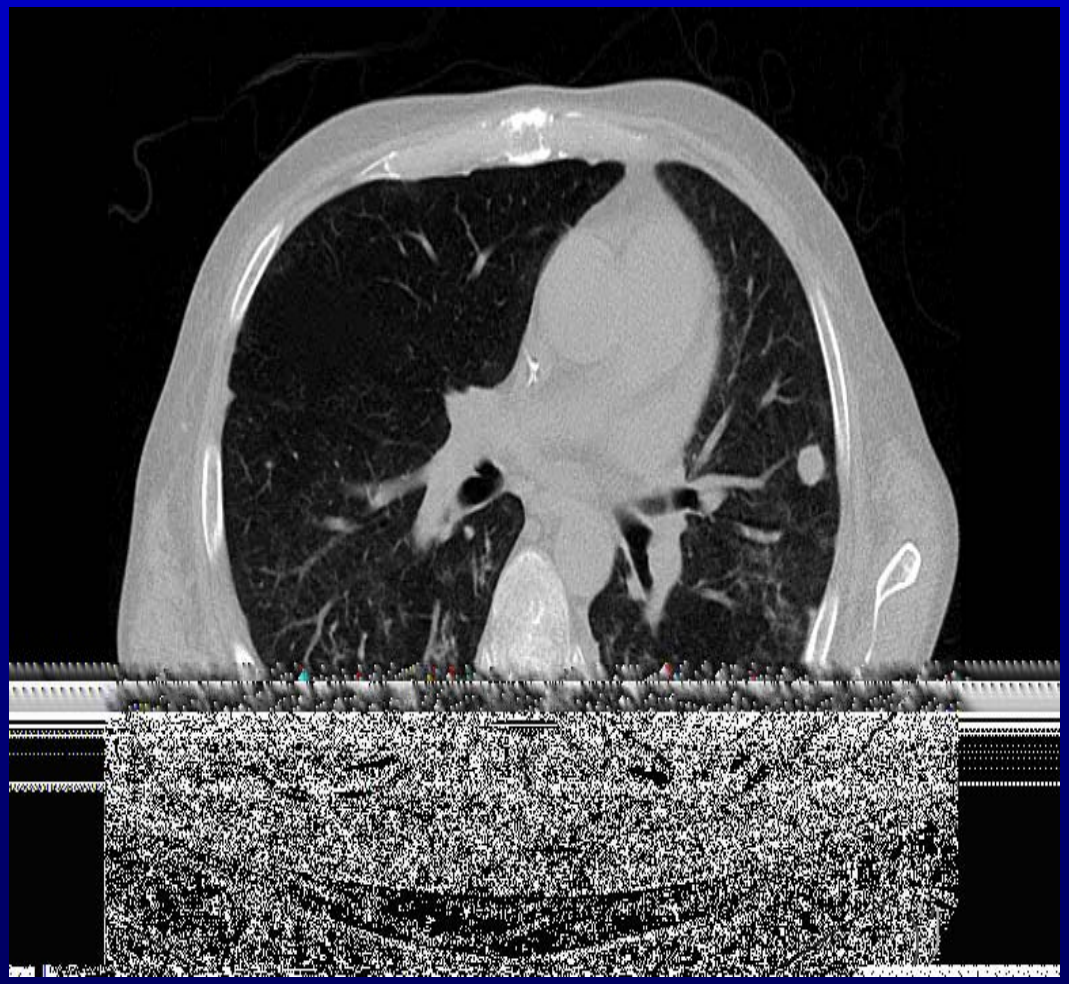
- Subjects:Induction chemo AML/MDS
- Open label, MD Anderson Hospital
- Caspofungin: 50 mg/d iv (106 Pts)
- Itraconazole: 200 mg/d iv (86 Pts)
- Duration: 21 days (median)

	Caspofungin	Itraconazole
Without IFI	55 (52)	44 (51)
With IFI	5	7
Death 2° IFI	2	4
Adverse Events	≡	≡

* IV Itraconazole: No cardiovascular toxicity

Mattiuzzi GN, et al. *Antimicrob Agents Chemother*. 2006;50:143-147.

Micafungin Prophylaxis : Breakthrough Aspergillosis



- 36 y/o man-CML
- Allotransplant; GI, liver – GVHD
- GVHD Rx: steroids/etanercept/mesenchy. stem cells
- Prophylaxis with Micafungin 150mg qd
- Asp GM 4d : 0.2
  21d : 2.1

Caspofungin: Breakthrough IA

156 HSCT recipients, ’04 – ’07

Breakthrough IA, on Caspofungin (≥ 6 days) 9 (6%)

Duration of Caspofungin (empiric)	7-197 d
Proven/Probable	9
A.fumigatus	3
A. ustus	1
A. nidulans	1
Death with or from IA	5
Caspo. Resist isolates	2 (of 4)

Madureira A et al, ICAAC 2007 (M-1166)

Polyenes (Amphotericin B): Prophylaxis

- Oral suspension/lozenges: Ø reduction in IFI
- Low dose AmB or alternate day AmB:
  - ↓ effect/toxicity[1]
- Aerosol AmB vs Placebo: Prolonged neutropenia[2];
  - Aspergillosis: 4% vs 7% (*P* = NS)
- Lipid formulations
  - Liposomal AmB (vs placebo/azole)[3]: Unsatisfactory
  - AmB Colloidal Dispersion[4]: Toxicity
  - Aerosol ABLC/AmB : ↓ rate of IFI: Ø pneumonia; ABLC better tolerated[5]
- Issues: Toxicity/Cost/Route/? Efficacy
  - Inhalational – ? promise

[1]Wolff SN, et al. *Bone Marrow Transplant.* 2000;25:853-859.
[2]Schwartz S, et al. *Blood*, 1999;93:3654-3861.
[3]Mattiuzzi GN, et al. *Cancer*. 2003;97:450-456.
[4]Timmers GJ, et al. *Bone Marrow Transplant. 2000;25:879-884.*
[5] Drew RW et al, *Transplantation* 77:232-7, 2004.

SECONDARY PROPHYLAXIS

Older concept: IA is an absolute contraindication for HSCT….Not true

Prior IA → Secondary prophylaxis is routine with chemotherapy/HSCT

Which drug??

2006 (Blood): 129 pts with history of IA/SCT, Relapse 27 (22%)

Vori prophy : 12% relapse

Other Prophy : 22% relapse

Martino R, *Blood*, 2006

Pre-emptive Strategy: On Fluconazole Prophylaxis

Neutropenic Patients – Thrice weekly serum Asper. galactomannan (GM) test

No antimold drugs for fever, unless

Antigenemia on consecutive specimens, OR

CT scan abnorm. + Aspergillus in BAL

Antifungal therapy reduced by 78%; missed non-asperg. IFI.

Maertens et al, CID, 2005

Problems with GM

- ↓ sensitivity (<50%), if prevalence 5% to 10%
- Antimold prophylaxis increasing
- False positives (children, drugs, cross reactivity)
- Testing three times weekly - ? practical

Prophylaxis Limitations

Itra.	Vori.	Posa.
•Oral intolerability	•Bkthru (*Cglab*, *Zygo*)	•Poor Bioavail
•↑ LFT	•↑ LFT	•High Fat Intake
•? Flucon ® Candida	•Flucon ® Cand.	•Ø IV Form
• Renal Dis : ? IV form	•Renal Dis. : ? IV form	•Flucon® Candida
•Ø Zygomycetes	•Ø Zygomycetes	•↑ LFT
•Drug Interaction	•Drug Interaction	•Drug Interaction
•? Need for Levels	•? Need for Levels	•? Need for Levels

Prophylaxis Limitations

Echinocandin

- Static vs. Asperg.
- Ø Oral Form
- Ø Zygo Fusar/Scedosp.

Polyene

- Nephrotoxicity
- Ø Oral Form
- Inhalation – ??
- Asp terreus

BACK TO THE CASE REPORT……

Summary : Post Allogeneic Stem Cell Recip. with GVHD: Vori. prophy → Breakthrough Aspergillosis

Reasons for Breakthrough

- Decreased Serum Vori. Level[1]
- Exposure to Aspergillus spores in Community
- Resistance – Rare
  - Primary – A.nidulans/A.lentulus
  - Secondary – A.fumigatus
- Mixed Infection
- Increased Immunosuppression ('Host Failure')

[1]Pascual A, *Antimicrob Agents Chemother* 51:137, 2007.

Treatment of Prophylaxis Failure: Change Regimen

- Switch from voriconazole to posaconazole
- Switch from voriconazole to lipid AmB
- Switch from voriconazole to an echinocandin

Treatment of Prophylaxis Failure: Combination Therapy

- Azole plus echinocandin
- Polyene plus echinocandin

Treatment Upon Prophylaxis Failure: Dose Adjustment

- Check voriconazole level
- Adjust dose

How do you manage IA prophylaxis failure?

a. Switch from voriconazole to posaconazole
b. Switch from voriconazole to lipid AmB
c. Switch from voriconazole to an echinocandin
d. Initiate combination therapy with an echinocandin
e. Adjust the voriconazole dose