Antifungal Prophylaxis in AML Patients Receiving Intensive Induction Chemotherapy: Prospective Observational Study from the Acute Leukemia French Association (ALFA) Group

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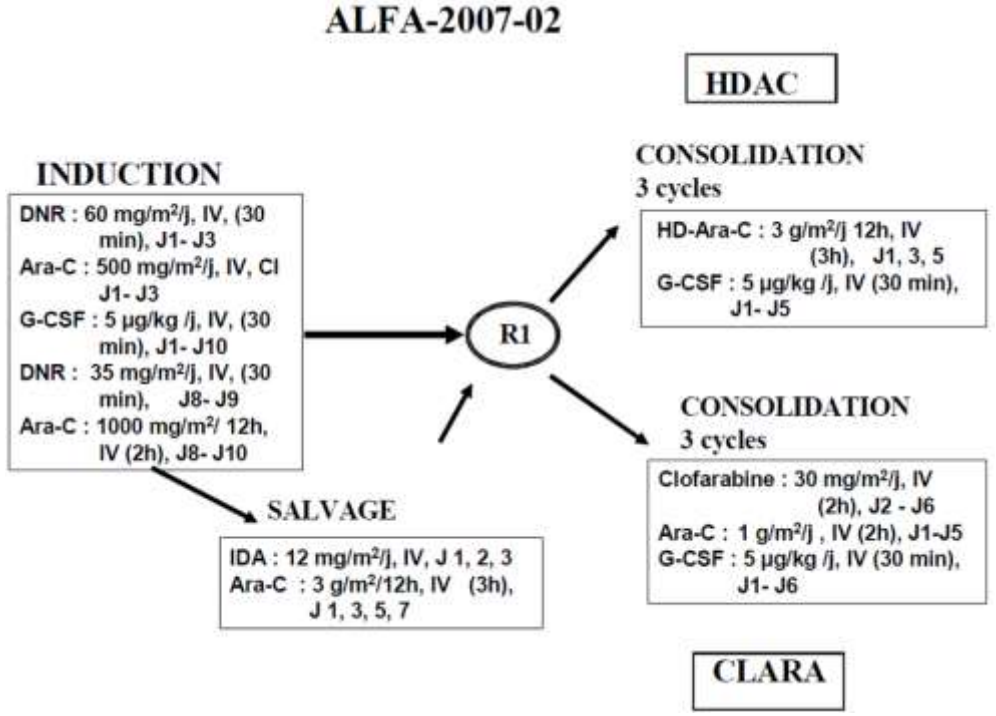
Introduction & Objectives

Prospective observational study on antifungal (AF) prophylaxis used in a prospective clinical trial of intensive chemotherapy within the Acute Leukemia French Association
(ALFA 0702 study, ClinicalTrials.gov Identifier: NCT00932412)



Objectives

- Describe the different strategies used for IFI prophylaxis
- Calculate the cumulative incidence of IFIs according to different strategies
- Evaluate the consistency between IFI assessment by the centers and that of independent experts
- Evaluate the impact of AF drugs dosage on IFI incidence
- Evaluate overall survival and IFI-related death

Material & Methods

Protocol Recommendation

Prophylaxis by posaconazole oral suspension 200 mg three times / day from D4 after induction chemotherapy until neutrophils recovery according to the ECIL recommendations

IFI Classification

- **IFI were initially classified by local investigators according to the modified EORTC criteria**
- **Reassessment and validation by 2 external experts was performed after referring to CRF and imagery**

IFI prophylaxis duration

Were considered as receiving AF prophylaxis, only patients who received an antifungal prophylaxis for a minimum duration of 7 days and not beyond day 10 after the onset of induction chemotherapy

Results

- 677 AML patients included in the ALFA 0702 study
- 45% males, median age= 46 years (18-60)
- Prognosis: favorable (23%), intermediate (53%) unfavorable (14%)
- Among the 677 patients, 383 (57%) have received posaconazole prophylaxis
- Posaconasole was administered after a median of 3 days following induction
- Median duration of posaconazole administration: 25 days (7-253)
- The vast majority of patients were in protected environment

Results

We distinguished 4 groups:

- **Group 1 :** ***Patients without prophylaxis N= 203 (30%)***
- **Group 2 :** ***Posaconazole alone N= 241 (36%)***
- **Group 3 :** ***Posaconazole plus other prophylaxis N= 142 (21%)***
- **Group 4 :** ***Patients with other prophylaxis N= 91 (13%)***
  - *Cancidas: 54%*
  - *Ambisome 25%*
  - *Fluconazole: 11%*
  - *Voriconazole: 10%*

Results: IFI Incidence

- **Invasive aspergillosis (IA) : N= 72**

  34 (47%) possible, 38 (53%) probable /proven

- **Invasive Candidosis (IC) : N= 17**

  All probable/proven

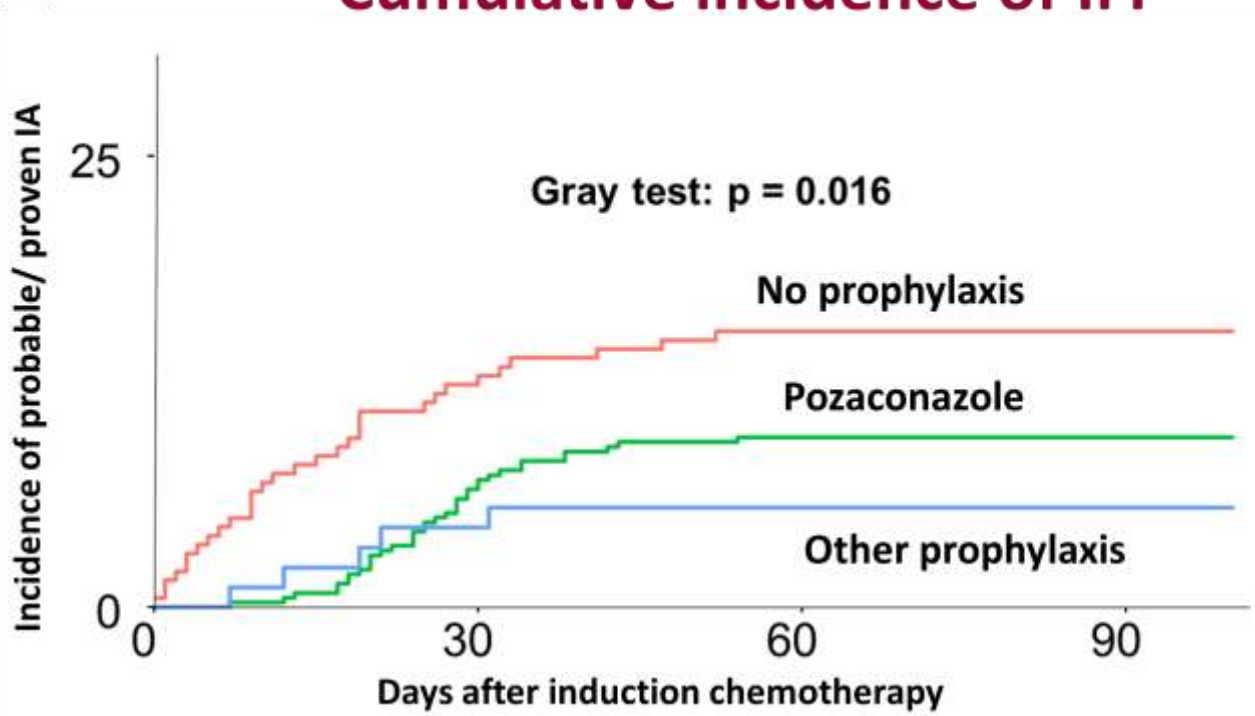
- **Other Invasive Mycosis (IM) : N= 7**

  1 possible, 6 probable/proven

Results: IFI Incidence

- **Cumulative incidence (CI) of IFI**
  - 2.4% @ d10 (IA: 2.4%, IC: 0%, IM: 0%)
  - 11.2% @ d30 (IA: 8.4%, IC: 2%)
  - 14.2% @ d60 (IA: 10.6%, IC: 2.5%, IM: 1%)
  - 14.2% @ d100 (IA: 10.6%; IC: 2.5%; IM: 1%)
- **CI of probable/proven IA @ d60**
  - 8.37% in group 1 (No prophylaxis)
  - 4.7% in groups 2 & 3 combined (posaconazole)
  - 3.3% in group 4 (other prophylaxis)

Cumulative incidence of IFI



- **Median time for IFI occurrence:**

Posaconazole
- *22 days (7-50) for IA*
- *18 days (15-60) for IC*
- *26 days (13-28) for IM*

Other Prophylaxis
- *10 days (3-180) for IA*
- *8 days (3-32) for IC*
- *21 days (10-32) for IM*

Results: IFI Classification

Among patients with IFI (72 IA, 17 IC and 7 IM): reevaluation of files/scanners for 37 patients

Evaluation Concordance: 67 %

(p=0.219) Pearson's Chi2 Test with Monte-Carlo method

	IA (n=72)	IC (n=17)	IM (n=7)
Not classified -> Possible	1 (1%)	-	1 (14%)
Not classified -> Probable/Proven	2 (3%)	15 (88%)	6 (86%)
Possible -> Possible	20 (28%)	-	-
Possible -> Probable/Proven	8 (11%)	1 (6%)	-
Probable/Proven -> Possible	13 (18%)	-	-
Probable/Proven -> Probable/Proven	28 (39%)	1 (6%)	-

Results: Posaconazole dosage

- Among 383 patients who received posaconazole, 92 (24%) were dosed
- Among the 92 patients dosed : 10 IFI were observed

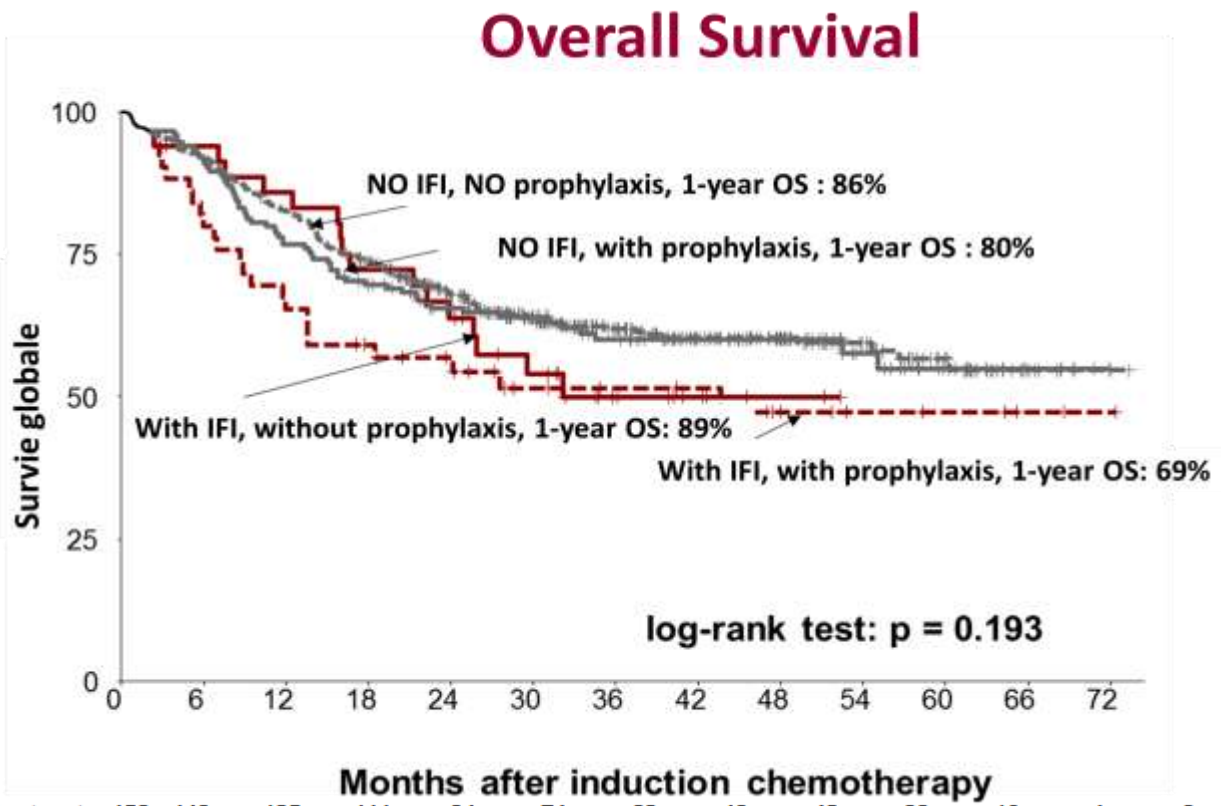
  8 IA (6 possible, 2 probable/proven), 1 IC probable/proven, 1 IM probable/proven

	< 0.5 mg N=18	0.5 – 0.7 mg N=44	> 0.7 mg N=20
Aspergillosis	6	2	0
Candidosis	1	0	0
Mycosis	1	0	0
	44.5%	4.5%	0%

OR: 0.71 [95% IC: 0.50 - 1.65], p=0.06

Results: Overall Survival

There was no significant difference in terms of patients and disease characteristics between the different prophylaxis groups at study inclusion



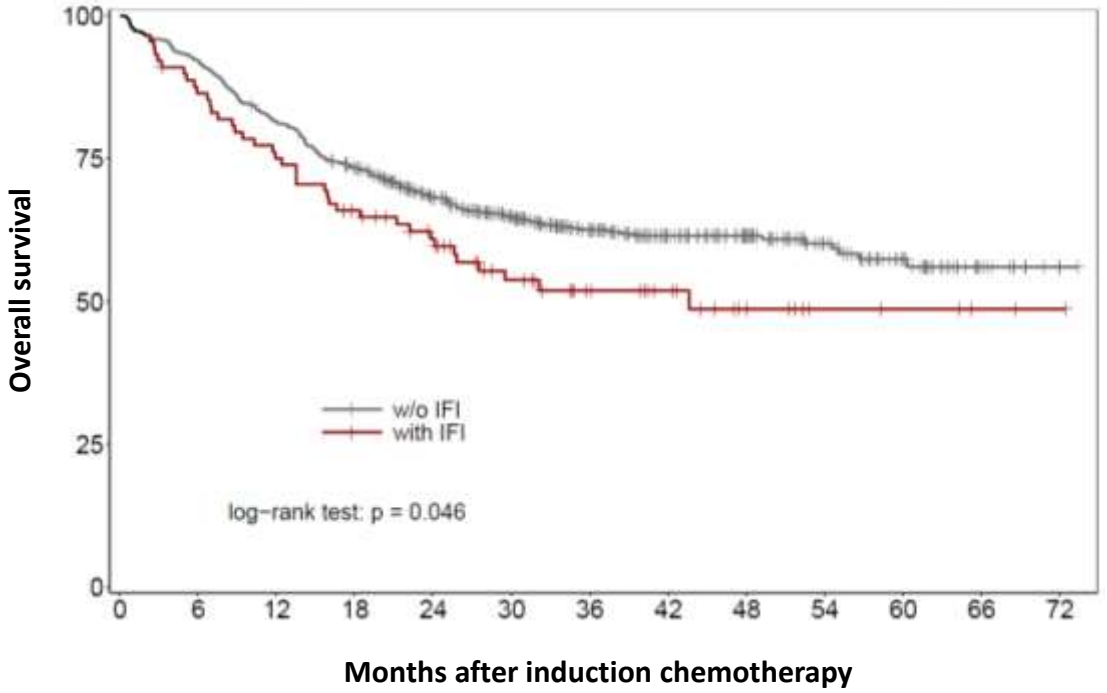
w/o IFI w/o treatment	156	148	125	111	94	74	62	48	40	22	13	4	0
w/o IFI with treatment	412	394	353	312	251	196	144	103	75	50	32	9	2
with IFI w/o treatment	38	36	33	28	23	17	9	5	2	0	0	0	0
with IFI with treatment	48	40	33	28	24	17	14	13	8	5	4	2	1

Results: Overall Survival

Median follow-up: 27.5 months (0.4-73.4), 418 patients alive & 259 (38.3%) dead

5.4% IFI-related death

Landmark analysis from day 60



Multivariate analysis on day 100 mortality:

- **Unfavorable cytogenetics: HR = 3.34 (1-11.20) p = 0.05**
- **IFI: HR = 5.63 (2.62-12.08) p <0.001**

Conclusions

- **Despite the protocol recommendations, this study shows that ECIL recommendations are followed only in 57% of cases**

- **AF prophylaxis has a significant impact on IFI incidence, a direct impact on overall survival with an IFI-related mortality rate of 5.4%**

- **Posaconazole dosage has demonstrated its importance for the prevention of IFI**

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