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CLARITY

Clinical implications of azole-resistant aspergillosis in hematological malignancy: a multi-center study

Danila Seidel[1], Oliver A. Cornely[1], Marouan Zarrouk[1], Philipp Köhler[1], Jacques F. Meis[2], Jon Salmanton-Garcia[1], J. Janne Vehreschild[1], Martin Christner[3], Stefanie Gräfe[1], Iker Falces-Romero[4], Agustín Reséndiz Sharpe[5], Katrien Lagrou[5], Johan Maertens[5], Zdenek Racil[6], Barbora Weinbergerova[6a], Maricela Valerio[7], Patricia Muñoz[7], Ola Blennow[8], Blandine Rammaert-Paltrie[9], Alen Ostojic[10], Yohann Le Govic[11], Cornelia Lass-Flörl[12], Susann Rössler[13], Karin van Dijk[14], Nick de Jong[14], Jörg Steinmann[15], Guillaume Desoubeaux[16], Nael Alakel[17], Nikolay Klimko[18], Enrico Schalk[19], Marie-Pierre Brenier-Pinchart[20], Carolina Garcia-Vidal[21], Anne Bergeron[22], Sung-Yeon Cho[23], Willem J.G. Melchers[24], Maria J.G.T. Vehreschild[1,25], Paul E. Verweij[24]; for the CLARITY group.

Background

Survival of patients with invasive aspergillosis (IA) has improved in recent years mainly due to the availability of azole antifungal drugs. Emergence of azole resistance in *Aspergillus fumigatus* has been noted around the world, challenging patient management. Resistance mechanisms, with differing degrees of cross-resistance, are mainly characterized by point mutations in the *cyp51* gene encoding the target for azoles.[1]

Increased mortality has been noted due to high probability of azole treatment failure in patients with azole-resistant isolates. However, the clinical implications of azole-resistant (**arIA**) compared to azole-susceptible IA (**asIA**) remain less well studied.

Objectives

- Assess clinical implications of IA caused by azole-susceptible vs. azole-resistant *A. fumigatus*
- Determine the efficacy of antifungal therapy in patients with azole-resistant IA (**arIA**) vs. azole-susceptible IA (**asIA**)

Inclusion criteria

- Patients with a hematological malignancy
- Proven or probable IA[2] caused by *A. fumigatus* diagnosed in 2010 or later
- Fungal clinical isolate AND/OR susceptibility results confirming azole-resistance AND/OR genetic alterations associated with azole-resistance identified

Methods

1. **Retrospective, anonymized documentation of clinical data** in a web-based case report form accessible through www.clinicalsurveys.net
   - Demographics, underlying disease
   - Diagnostics, antifungal susceptibility
   - Antifungal therapy, response and outcome
2. **Collection of clinical fungal isolate** for
   - Antifungal susceptibility testing (EUCAST)
   - Analysis of resistance mechanisms (*cyp51A*)

Results

Table 1. Characteristics of 31 arIA and 156 asIA cases

	arIA n=31		asIA n=156		*P*
	N	%	N	%	
Male (%)	22	71.0	102	65.4	
Adult (≥17 years)	29	93.5	149	95.5	
Underlying conditions/Risk Factors °					
Malignancy					
Acute Leukemia	13	41.9	61	39.1	
Chronic Leukemia	2	6.5	14	9.0	
Lymphoma	4	12.9	39	25.0	
Multiple Myeloma	2	6.5	13	8.3	
MDS	5	16.1	18	11.5	
Other[1]	5	16.1	11	7.1	
Chemotherapy	26	83.9	149	95.5	*
allogeneic HSCT	18	58.1	61	39.1	
autologous HSCT	4	12.9	14	9.0	
Comorbidities §	9	29.0	58	37.2	
Neutropenia	17	54.8	93	59.6	
<10 days	3	9.7	23	14.7	
≥10 days	14	45.2	70	44.9	
ICU stay	8	25.8	26	16.7	
Sites of infection					
Lung	31	100.0	145	92.9	
CNS	3	9.7	7	4.5	
Other[2]	3	9.7	17	10.9	
Disseminated	4	12.9	11	7.1	

Table 2. Antifungal treatment and outcome

	arIA n=31		asIA n=156		*P*
	N	%	N	%	
Antifungal prophylaxis	9	29.0	22	14.1	
Azole	9	29.0	18	11.5	
Other	0	0.0	6	3.8	
Length overall, days	92 (68 - 183)		16 (10 - 35)		*
Treatment strategy					
AFT + surgery	0	0.0	12	7.7	
AFT only	30	96.8	139	89.1	
Surgery only	0	0.0	1	0.6	
None	1	3.2	4	2.6	
Antifungal treatment					
Amphotericin B	24	77.4	76	48.7	*
Voriconazole	20	64.5	120	76.9	
Other azoles	8	25.8	42	26.9	
Caspofungin	7	22.6	40	25.6	
Other echinocandins	3	9.7	9	5.8	
Length overall, days	27 (10.5 - 53)		46 (16 - 129)		
Treatment response and mortality					
Success	7	22.6	84	53.8	*
Failure	21	67.7	59	37.8	
Unknown response	3	9.7	13	8.3	
Mortality	24	77.4	84	53.8	*
Follow-up, days [median (IQR)]					
Overall	23 (5 - 66)		83 (19 - 255)		
Dead overall	17 (4 - 33)		30 (8 - 119)		*

* P value <0.05, if not marked *P* value was >0.05

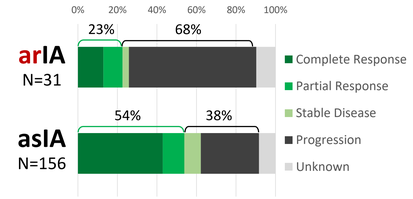
Abbreviations: Abbreviation: AFT, systemic antifungal treatment; ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; HSCT, Hematopoietic stem-cell transplantation; ICU, Intensive care unit; MDS, Myelodysplastic Syndrome

Table 1. Neutropenia before diagnosis of invasive aspergillosis; [1] **Underlying condition (Other)**: Myelodysplastic syndrome, Aplastic Anaemia, Myelofibrosis, Evans syndrome; § Comorbidities include: chronic liver disease, chronic renal disease, chronic pulmonary disease, diabetes mellitus, recent viral pneumonia, and rheumatic/autoimmune diseases; [2] **Site of infection (Other): arIA:** Peritoneum, bowel (1), eye (1), heart (1); **asIA**: paranasal sinus (7) + eye (1), deep Soft Tissue (5), Liver + spleen (3), kidney + GIT (1)

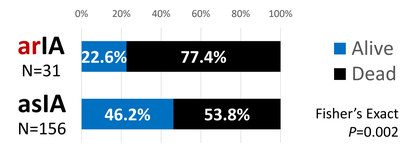
Table 2: Length of antifungal use for prophylaxis and treatment provided in days, median (interquartile range); **Treatment response**: Success (complete or partial response), Failure (stable disease, progression)

Figure 1. Clinical Response at Final Assessment and Patient Outcome

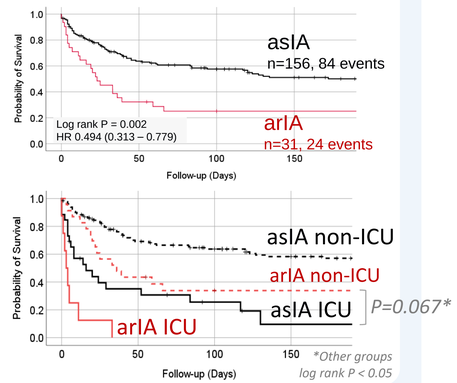
Overall response to antifungal treatment at final assessment



Final Outcome

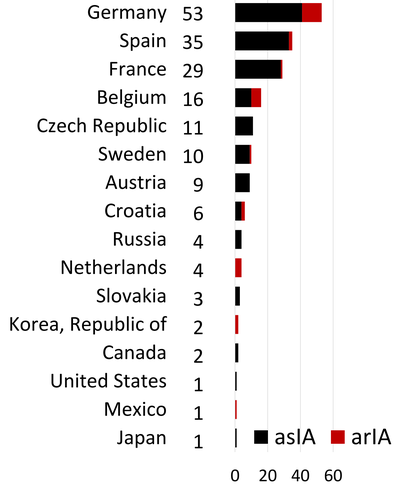


Kaplan Meier survival curves for all patients (top) and patients treated at the ICU or other wards (non-ICU) (bottom)



Number of cases included in CLARITY from 16 countries worldwide

Ratios are not representative for incidences in the country.



Summary and Conclusion

- Most common risk factor for **arIA** and **asIA** in hematological oncological patients was acute leukemia (Table 1)
- Mortality was highest in patients with **arIA** treated in the ICU (100% vs. 80.8% in ICU patients treated for **asIA**, *P*=0.309)
  - Median survival time was 3 days (95%CI 0.228 – 5.772) for **arIA** and 16 days (95%CI 0 – 34.025) for **asIA** patients treated in the ICU; HR 0.346 (95%CI 0.146 – 0.824) in favor of **asIA**
- Azole resistance in *A. fumigatus* was an independent predictor for mortality in patients with underlying malignancy

Medizinische Fakultät der Universität zu Köln

Affiliations [1] University Hospital of Cologne, ECMM Excellence Center, Cologne, Germany; [2] Canisius Wilhelmina Hospital, *Nijmegen*, The Netherlands; [3] Institute for Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4] Hospital Universitario La Paz, Madrid, Spain; [5] KU Leuven, Leuven, Belgium; [6] Institute of Hematology and Blood Transfusion, Prague, Czech Republic; [6a] Faculty Hospital Brno, Brno, Czech Republic; [7] Hospital General Universitario Gregorio Marañón. Clinical Microbiology and Infectious Diseases Department, Madrid, Spain; [8] Karolinska University Hospital, Department of Infectious Diseases, Stockholm, Sweden; [9] CHU Poitiers, Infectious Disease, Poitiers, France; [10] University Hospital Centre Zagreb, Zagreb, Croatia; [11] University Hospital Angers, Angers, France; [12] Medical University of Innsbruck, Innsbruck, Austria; [13] Technische Universität Dresden, Institute of Medical Microbiology and Hygiene, Dresden, Germany; [14] Amsterdam UMC, location VUmc, The Netherlands; [15] Paracelsus Medical University, Nuremberg, Germany; [16] University of Tours, Tours, France; [17] University Hospital Dresden, Dresden, Germany; [18] North Western State Medical University, Saint Petersburg, Russian Federation; [19] Otto-von-Guericke University, Magdeburg, Germany; [20] Parasitology-Mycology, Centre hospitalier Grenoble Alpes, France; [21] Hospital Clinic, Department of Hematology, Barcelona, Spain; [22] Université Paris Diderot, APHP Saint-Louis Hospital, Paris, France; [23] Seoul St. Mary's Hospital, Division of Infectious Diseases, Seoul, South Korea; [24] Radboud University Medical Center, Nijmegen, The Netherlands; [25] Goethe University Frankfurt, Frankfurt am Main, Germany.

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