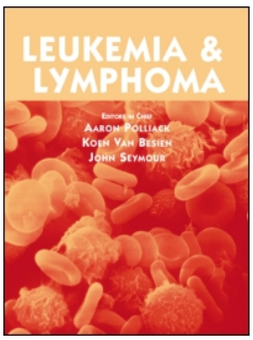

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

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To cite this article: Marco Sanna, Giovanni Caocci, Antonio Ledda, Federica Orrù, Claudio Fozza, Paola Deias, Gianni Tidore, Fausto Dore & Giorgio La Nasa (2017): Glucose-6-phosphate dehydrogenase deficiency and risk of invasive fungal disease in patients with acute myeloid leukemia, Leukemia & Lymphoma, DOI: 10.1080/10428194.2017.1312666

To link to this article: http://dx.doi.org/10.1080/10428194.2017.1312666

LEUKEMIA & LYMPHOMA, 2017
http://dx.doi.org/10.1080/10428194.2017.1312666

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ORIGINAL ARTICLE: CLINICAL

Glucose-6-phosphate dehydrogenase deficiency and risk of invasive fungal disease in patients with acute myeloid leukemia

Marco Sanna[a]*, Giovanni Caocci[a]*, Antonio Ledda[a], Federica Orrù[a], Claudio Fozza[b], Paola Deias[a], Gianni Tidore[b], Fausto Dore[b] and Giorgio La Nasa[a]

[a]Hematology Unit, Department of Medical Sciences and Public Health, Bone Marrow Transplant Center, R. Binaghi Hospital, University of Cagliari, Cagliari, Italy; [b]Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy

ABSTRACT

Invasive fungal diseases (IFD) are still a leading cause of morbidity and mortality in patients with acute myeloid leukemia (AML). Glucose-6-phosphate dehydrogenase is an enzyme that leads to the production of NADPH, required to destroy microorganisms in the respiratory burst reaction of white blood cells. We evaluated the role of G6PD deficiency in susceptibility of IFD in 108 AML patients undergoing intensive chemotherapy. In all, 28 patients harbored G6PD deficiency (G6PD−), whereas 80 were normal (G6PD +). Incidence of IFD was significantly higher in G6PD− patients compared to G6PD + patients (35.7% vs. 5%, $p = .0002$, OR = 10, 95% CI = 2.96–37.5). Higher risk of mold infections (17.9% vs. 5%, $p = .048$, OR = 4.1, 95% CI = 1.0–16.6) and *Candida* sepsis (17.9% vs. 0%, $p = .0009$, OR = 37.68, 95% CI = 2.0–707.1) was observed in G6PD − patients. The evaluation of G6PD activity may help to identify AML patients at higher risk of IFD, allowing to design more intensive surveillance and therapeutic strategies.

ARTICLE HISTORY
Received 5 February 2017
Revised 15 March 2017
Accepted 20 March 2017

KEYWORDS
G6PD; aspergillosis; *Candida*; acute myeloid leukemia; fungal infection

Introduction

Invasive fungal diseases (IFD) represent a leading cause of morbidity and mortality in patients with hematologic malignancies [1]. Patients at higher risk of IFD are those affected by acute myeloid leukemia (AML) receiving remission induction chemotherapy [2] or undergoing hematopoietic stem cell transplantation (HSCT) [3]. In AML patients, invasive fungal infections are primarily due to *Candida* spp or *Aspergillus* spp. IFD incidence in AML patients is around 12%, with an incidence of invasive candidiasis (IC) and proven\probable aspergillosis of 2.6–4.4% and 6–8%, respectively [4,5]. The risk of developing IFD in the immunocompromised host is influenced by several factors, such as genetic and environmental factors, patient performance status, and comorbidities [5]. The precise role of these factors remains to be elucidated and is currently still under active investigation.

Glucose-6-phosphate dehydrogenase (G6PD) is the most common human enzyme defect, affecting more than 400 million people worldwide. G6PD is a key enzyme in the pentose-phosphate pathway and the production of nicotinamide adenine dinucleotide phosphate (NADPH); this mechanism protects cells from oxidative stress and promotes neutrophil oxidative burst responses [6].

The inheritance of G6PD deficiency shows a typical X-linked pattern, in which males are hemizygous and can therefore have normal gene expression or be G6PD− deficient.

The clinical manifestations of G6PD deficiency are neonatal jaundice and acute hemolytic anemia episodes secondary to exogenous agents, such as drugs [7]. The role of G6PD deficiency in susceptibility to infections is controversial, with some reports suggesting an increased risk for the newborn or trauma patients to develop bacterial infections [8,9]. However, this observation has not been confirmed in prospective clinical trials [10,11]. To the best of our knowledge, the relationship between IFD and G6PD deficiency has never been investigated. The aim of the present study was to evaluate the role of G6PD deficiency in IFD onset in a cohort of AML patients undergoing chemotherapy or HSCT.

CONTACT Giovanni Caocci giovanni.caocci@unica.it Dipartimento di Scienze Mediche e Sanità Pubblica, Università di Cagliari, Ospedale "R. Binaghi", Via Is Guadazzonis, 3, Cagliari 09126, Italy
*These authors contributed equally to this work.

Methods

Study design

Patients diagnosed with AML from January 2012 to January 2015 at the Bone Marrow Transplant Center of the R. Binaghi Hospital, University of Cagliari, and the University Hospital Clinic in Sassari were prospectively enrolled in this study. The study protocol was approved by the institutional review board of each participating center. Treatment was based on ELN guidelines [12]. Patients were defined as having relapsing/refractory AML if relapse occurred during follow-up or in cases of induction chemotherapy refractory AML. *Performance status* was graded by the Eastern Cooperative Oncology Group (ECOG) scale [13]. Proven/probable IFD were defined according to the revised EORTC/MSG definitions published in 2008 [14]. Briefly, proven infection was diagnosed if histologic evidence of *Aspergillus* by biopsy from a sterile site, or positive culture from a sterile site; probable infection was instead diagnosed in presence of at least one clinical (e.g. halo sign), one host (e.g. neutropenia), and one mycological criteria (e.g. recovery of *Aspergillus* from culture of non-sterile site as BAL or sputum). Diagnostic workup was identical in the participating centers and included the following: nasal, pharyngeal, and rectal swabs at the time of admission; blood cultures and chest X-rays at onset of fever; Galactomannan assays twice a week, and computed tomography (CT) scan on the 4th to 7th day of fever. Additional examinations were based on clinical indications, for example, abdominal ultrasound scan, sinus or brain CT, skin biopsy, bronchoalveolar lavage, fundus examination.

Induction therapy was administered with one or more courses of the "3 + 7" regimen containing idarubicin (13 mg/m^2 from day 1 to 3) and cytarabine (100 mg/m^2 from day 1 to 7); consolidation therapy was performed with high-dose cytarabine (3 g/m^2 for 3 days). Primary refractory or relapsing patients were treated according to the FLAI scheme (fludarabine 30 mg/m^2 from day 1 to 5, cytarabine 2 g/m^2 from day 1 to 5, and idarubicin 13 mg/m^2 on days 1-3-5). Additional courses of therapy included the G-CLAC scheme (clofarabine 30 mg/m^2 from day 1 to 5, cytarabine 2 g/m^2 from day 1 to 5). Patients undergoing HSCT were conditioned with the TBF regimen (thiotepa 5 mg/kg on days -6 and -5; fludarabine 50 mg/m^2 on days -4, -3, and -2; and busulfan 3.2 mg/kg on days -4, -3, and -2). All patients undergoing remission induction chemotherapy received posaconazole prophylaxis. During consolidation chemotherapy, patients with no history of IFD underwent prophylaxis with Fluconazole; patients with a previous episode of IFD underwent secondary prophylaxis with voriconazole, posaconazole, or echinocandins according to clinical guidelines [15]. Patients undergoing HSCT conditioning chemotherapy underwent prophylaxis with Fluconazole; patients with active disease at transplantation or developing acute or chronic graft versus host disease (GvHD) underwent prophylaxis with posaconazole. Patients undergoing HSCT with a history of IFD were treated with voriconazole, posaconazole, or echinocandins as needed. Antibacterial prophylaxis was based on IDSA guidelines [15]. All patients underwent prophylaxis with Levofloxacin or Ciprofloxacin 500 mg bid from the first day of chemotherapy until neutrophils $>1000/mm^3$. This strategy was adopted for induction and consolidation courses. For patient undergoing HSCT, Levofloxacin 500 mg/day was used as prophylaxis from day -6 until neutrophils $>1000/mm^3$.

Microbiologically documented infection (MDI) was defined as isolation of the etiologic agent by culture or biopsy. Blood cultures were processed using the automated BACTEC system (Becton Dickinson Diagnostic Instruments, Sparks, MD). Clinically documented infection was defined as a site of infection on physical examination without isolation of the etiologic agent. The median follow-up was 32 and 34 months for patient with G6PD deficiency and normal, respectively. The infectious outcomes were assessed at the end of each hospitalization, and every 2 months for patients at home.

G6PD determination

G6PD activity was determined before starting treatment using the G6PD/6PGD Automatic Analyzer (KUADRO, Nurex SRL, Rome, Italy). G6PD activity was expressed as the ratio between G6PD and 6PDG activities. Patients with enzyme activity levels $<10\%$ were classified as G6PD deficient (G6PD−). In consideration of the potential interference between the G6PD activity assay and hyperleukocytosis (frequently recorded at diagnosis in AML), patients with a white cell count (WBC) $> 20{,}000/mm^3$ and G6PD activity between 10% and 85% were evaluated a second time for G6PD activity after chemotherapy and normalization of the WBC count to assess the true G6PD status. Because of X-inactivation, heterozygous females with G6PD activity $\geq 10\%$ were considered to be without the enzymatic defect and classified as G6PD+.

Statistics

Incidence of IFD was the primary endpoint of the present study. Secondary endpoints were the impact of

G6PD deficiency on the incidence of *Candida* sepsis, mold infections, bacterial MDI, gram-positive or gram-negative infections, CDI, leukemia-free survival (LFS), overall survival (OS), infection-related death. The independent variables such as sex, age, G6PD activity, ECOG performance status, recent house renovation, BMI ≥30, chronic obstructive pulmonary disorder (COPD), and diabetes were analyzed in univariate analysis with the chi-squared test. Significant differences were calculated using Fisher's two-sided exact test or Pearson's chi-squared test, as appropriate. Only *p* values of less than .05 were considered to be statistically relevant.

Results

Patients

In all, 130 consecutive patients with a diagnosis of AML were analyzed over a period of 42 months. Four patients for whom G6PD activity at diagnosis was unavailable because of a technical problem were excluded from the study. Other two patients were excluded because of acute promyelocytic leukemia and early death. In all, 16 patients were excluded because they are not eligible for intensive chemotherapy. Altogether, 22 patients were excluded; analysis was performed on the remaining 108 patients. Of these patients, 28 (26%) were G6PD− and 80 (74%) were G6PD+. No significant differences were found between the two groups for sex, age, courses of chemotherapy, disease evolution, and median follow-up. The clinical features of the patients are reported in Table 1. Overall, 14/108 (13.0%) proven or probable IFD were recorded: five cases (4.6%) of Candida sepsis were identified. Nine (8.3%) mold infections were also recorded. Additionally, 24 cases (22.2%) of bacterial MDI were reported: 14 (13.0%) were caused by gram-positive and 10 (9.2%) by gram-negative bacterial strains. Furthermore, 39 (36.1%) infections were recorded as CDI. Overall, 68 infectious events occurred in 64 patients, with a cumulative incidence of 59.2%.

Invasive fungal disease and G6PD status

No association was found between IFD and COPD, diabetes, age, sex, performance status, recent house renovation, or BMI. A modest, although not statistically significant, trend was observed for IFD and relapsing/refractory disease ($p = .06$). The incidence of IFD was significantly higher in G6PD− patients compared to G6PD + patients (35.7% vs. 5%, $p = .0002$, OR = 10.5, 95% CI = 2.96–37.5, Table 2). This difference was not influenced by the allogeneic stem cell transplantation procedure. This is supported by the fact that also analysis performed before HSCT showed a significantly higher incidence of IFD in G6PD− patients ($p = .0006$, OR = 9, 95% CI = 2.5–32.4, Table 2). Interestingly, we only observed one case of IFD after HSCT in a

Table 2. Incidence of invasive fungal disease in acute myeloid leukemia patients.

Risk factors	IFD ($n = 14$) *n* (%)	Non-IFD ($n = 94$) *n* (%)	*p* Value
Diabetes			
Yes	3 (11.5)	23 (88.5)	
No	11 (13.4)	71 (86.6)	ns
Age			
>50	1 (9.1)	4 (66.7)	
<50	13 (13.4)	90 (89.8)	ns
ECOG ≥2			
Yes	2 (33.3)	4 (66.7)	
No	12 (10.2)	90 (89.8)	ns
Relapsing/refractory disease			
Yes	13 (16.9)	64 (83.1)	
No	1 (3.2)	30 (96.8)	ns
COPD			
Yes	0 (0)	4 (100)	
No	14 (13.5)	90 (86.5)	ns
House renovation	0 (0)	3 (100)	
Yes	14 (13.3)	91 (86.6)	ns
No			
BMI <30	12 (13.0)	80 (87.0)	
BMI >30	2 (12.5)	14 (87.5)	ns
G6PD+	4 (5.0)	76 (95.0)	
G6PD−	10 (35.7)	18 (64.3)	$p = .0002$
Censoring analysis pre-HSCT			
G6PD+	4 (5.0)	76 (95.0)	
G6PD−	9 (32.1)	19 (67.9)	$p = .0006$

IFD: invasive fungal disease; ECOG: Eastern Cooperative Oncology Group performance status score; COPD: chronic obstructive pulmonary disorder; BMI: body mass index; HSCT: allogeneic hematopoietic stem cell transplantation; G6PD−: glucose-6-phosphate dehydrogenase deficiency.

Table 1. Clinical characteristics of patients enrolled in the study.

Clinical variables	G6PD− ($n = 28$)	G6PD+ ($n = 80$)	*p* Value
Age, median (range)	63 (27–82)	62 (23–84)	ns
Sex			
Male, *n* (%)	18 (64.3)	48 (60.0)	ns
Female, *n* (%)	10 (35.7)	32 (40.0)	
Chemotherapy + Allo-HSCT, *n* (%)	4 (14.3)	19 (23.7)	ns
Median follow-up, months	32	34	ns
Relapsing/refractory disease ≥2 lines of therapy, *n* (%)	20 (71.4)	57 (71.2)	ns
Ecog performance status <2, *n* (%)	27 (96.4)	75 (93.7)	ns
Hyperleukocytosis (WBC >40,000/mm^3), *n* (%)	8 (28.6)	27 (33.7)	ns

HSCT: hematopoietic stem cell transplantation; G6PD−/+: glucose-6-phosphate dehydrogenase deficiency or normal.

G6PD− patient transplanted from a G6PD-deficient sibling donor.

Species of fungal and bacterial infections

No differences were observed between the two cohorts of G6PD− and G6PD + patients for the incidence of microbiologically documented bacterial infections. Also the incidence of clinically documented infections was similar in the two groups (Table 3). We found five cases of *candida* sepsis in the G6PD− cohort and no cases of candidemia in the G6PD + cohort (17.9% vs. 0%, $p = .0001$, OR = 37.6, 95% CI = 2.0–707.1, Table 3). Focusing on mold infections (MI), we found a higher incidence in G6PD− compared to G6PD + patients (17.9% vs. 5%, $p = .048$, OR = 4.1, 95% CI = 1.02–16.67, Table 3). All isolated yeasts were non-*Albicans Candida* species (*Candida tropicalis*, *Candida guilliermondi*, *Candida glabrata*, and *Candida krusei* in two patients). Clinical data concerning *Candida* sepsis and other IFD, as well as clinical treatment, are given in Table 4. All patients who developed IFD were under posaconazole prophylaxis, except patient 10, who was diagnosed with probable aspergillosis after consolidation chemotherapy. Three of the five patients with invasive candidiasis (IC) died of *Candida* sepsis. The only two patients who survived IC had been treated with G-CSF and early catheter removal. Kaplan–Meier estimates of candidemia-free survival during follow-up showed a clear increase in risk for G6PD− patients (94.9% vs. 64.3%, $p < .0001$) (Figure 1).

Table 3. Characteristics of infections documented in the study.

Kind of infection	G6PD− ($n = 28$) *n* (%)	G6PD+ ($n = 80$) *n* (%)	*p* Value
No candida sepsis	23 (82.1)	80 (100)	
Candida sepsis	5 (17.9)	0 (0)	$p = .0001$
Candidemia only	3	0	
Multivisceral involvement (liver + kidney)	1	0	
Eye involvement	1	0	
No mold infection	23 (82.1)	76 (95.0)	
Mold infection	5 (17.9)	4 (5.0)	$p = .03$
Aspergillus pneumonia	2	2	
Fungal sinusitis-mastoiditis (not identified)	1	0	
Fungal pneumonia (not identified)	2	2	
Bacterial MDI	6 (18.7)	18 (19.6)	
No bacterial MDI	26 (81.3)	74 (80.4)	ns
Gram-positive	3 (50)	11 (61.1)	
Gram-negative	3 (50)	7 (38.9)	ns
CDI	12 (37.5)	27 (29.3)	
No CDI	20 (62.5)	65 (70.7)	ns

MDI: microbiologically documented infection; CDI: clinically documented infection; G6PD−/+: glucose-6-phosphate dehydrogenase deficiency or normal.

Clinical outcome

In our cohort of AML patients, 2-year leukemia-free survival (LFS) was 28.7%. No differences between G6PD− and G6PD + patients were found for overall survival (OS), 2-year LFS, and infection-related death (Table 5).

Table 4. Clinical features of IFD diagnosed in the study.

PN	Age/sex	G6PD status	Treatment	DP	DN	IFI	Level of certainty	CR/days from infection	Treatment	G-CSF	FRD
1	69/M	−	Re-induction (FLAI)	16	13	*C. krus*	Prov	No	Caspo; Second line L-Amb + Anidul	No	Yes
2	46/F	+	Re-induction (FLAI)	18	35	*Asp*	Prob	No	Voric	Yes	No
3	65/M	+	Re-induction (FLAI)	16	23	*Asp*	Prob	No	Voric; Second-line L-Amb	No	Yes
4	53/M	−	Re-induction (G-CLAC), post HSCT relapse	5	10	NI	Prob	No	L-Amb; Second-line Voric	Yes	Yes
5	68/M	−	Induction (3 + 7)	15	20	*C. krus*	Prov	Yes/12	Caspo	Yes	No
6	64/F	+	Induction (3 + 7)	17	29	NI	Prob	No	L-Amb; Second-line Voric	No	No
7	62/M	−	Induction (3 + 7)	24	36	*C. trop*	Prov	No	Anidul	No	Yes
8	25/M	−	Induction (3 + 7)	25	32	NI	Prob	No	L-Amb	No	No
9	53/F	−	Re-induction (G-CLAC)	14	25	*C. guill*	Prov	No	Caspof; Second-line L-Amb + Anidul	No	Yes
10	55/M	−	Induction (3 + 7)	19	25	*Asp*	Prob	No	Voric	Yes	No
11	47/M	−	Induction (3 + 7)	16	23	*Asp*	Prob	No	Voric	Yes	No
12	71/M	−	Induction (3 + 7)	25	33	NI	Prob	No	L-Amb; Second-line Voric	No	Yes
13	51/F	+	Follow-up post 1 consolidation (HD-ARA-C)	0	0	NI	Prob	No	Voric	No	No
14	63/F	−	Induction (3 + 7)	25	64	*C. glab*	Prov	Yes/10	Caspo	Yes	No

PN: patient number; G6PD−/+: glucose-6-phosphate dehydrogenase deficient or normal; DP: duration of antifungal prophylaxis; DN: duration of neutropenia; IFD: invasive fungal disease; CR: catheter removal; G-CSF: granulocyte stem cell factor; FRD: fungal-related death; M: male; F: female; FLAI: fludarabine, cytarabine, idarubicin; HD-ARA-C: high-dose cytarabine; G-CLAC: clofarabine, cytarabine; HSCT: allogeneic hematopoietic stem cell transplantation; *C. krus*: *Candida krusei*; NI: not identified; *C. trop*: *Candida tropicalis*; *C. guill*: *Candida guilliermondi*; *C. glab*: *Candida glabrata*; *Asp*: *Aspergillus species*; Prov: proven; Prob: probable; Caspo: caspofungin; Anidul: anidulafungin; L-Amb: lyposomal amphotericin-B; Voric: voriconazole.

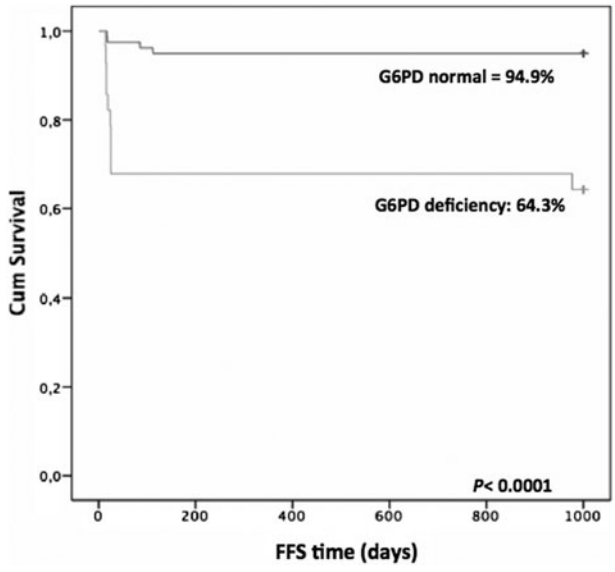

Figure 1. Fungal-free survival (FFS) in two groups of acute leukemia patients according to G6PD status.

Table 5. Clinical outcome of patients enrolled in the study.

	G6PD− (*n* = 28) *n* (%)	G6PD+ (*n* = 80) *n* (%)	*p* Value
Overall survival	10 (35.7)	28 (52.2)	ns
LFS	8 (28.6)	23 (28.8)	ns
IFRD	6 (21.4)	10 (12.5)	ns

LFS: leukemia-free survival; IFRD: infection-related death; G6PD−/+: glucose-6-phosphate dehydrogenase deficiency or normal.

Discussion

To the best of our knowledge, this is the largest cohort of AML patients investigated for association between fungal infections and G6PD deficiency. We observed that G6PD activity influenced the risk of developing IFD. In particular, G6PD enzyme deficiency seems to significantly increase the risk of *Candida* sepsis and mold infections. Several studies have identified risk factors for developing IFD in hematological disorders: patients with AML or undergoing HSCT were the categories with the highest risk [1,2,5,16]. Several modifiable and non-modifiable risk factors are associated with an increased risk for IFD [1], but only recently a prospective study identified body weight, recent house renovation, kind of job, and COPD as the variables associated with mold infections [4]. We did not find a correlation between these pre-chemotherapy variables and the onset of IFD. In our study, the cumulative incidence of proven/probable IFD was 11.3%, which is lower in comparison to the reports of other authors [4]. This discordance may be attributable to differences in the design of the studies (multicentric vs. monocentric), clinical approach, radiological evaluation, and local epidemiology. An interesting finding in our study was the higher incidence observed for *Candida* sepsis, with all cases diagnosed in G6PD− patients. It is important to mention that Candida sepsis is a proven infection and that the isolation of the yeast is an automated process. It follows that the higher incidence observed in our cohort with respect to other studies [1,4,5] cannot be explained by differences in clinical approaches or radiological evaluation. Instead, it is possible that this difference may be linked to differences in immune response against fungal species. The G6PD enzyme catalyzes the first reaction in the pentose phosphate pathway, thereby providing reducing power to cells in the form of NADPH that is essential to NADPH oxidase enzyme activity [6]. It has been shown that patients affected by chronic granulomatous disease (CGD), an inherited immunodeficiency disorder characterized by defective functioning of NADPH oxidase enzyme in phagocytes, are exposed to recurrent infections by catalase-positive organisms [17]. *Candida* and *Aspergillus* species both express catalase enzymes; hence, it is likely that G6PD− patients with chemotherapy-induced neutropenia are particularly vulnerable to these germs [18]. A previous study of the G6PD *Mediterranean* variant showed that G6PD-deficient granulocytes display a reduced function in-vitro ranging from 25% to 33% [19,20]. Nevertheless, in-vitro response of G6PD− granulocytes against *Aspergillus* and *Candida* strains has never been analyzed; this important aspect deserves further investigation. We did not find any association between G6PD activity and infection-related death, but this result could be biased by the small size of the patient cohorts. A strength in our study was the homogeneity of the two cohorts: all patients underwent the same kind of treatment and antifungal prophylaxis.

In our cohort, surveillance was performed twice weekly using the Galactomannan assay; however, this test is only useful for the detection of invasive aspergillosis [21]. Our data suggest that G6PD− patients are exposed to a higher risk of yeast infections. Assays such as β-D Glucan, Mannan/Antimannan Antigen Antibodies, and *Candida* PCR seem to be more useful in the detection and diagnosis of *Candida* sepsis [22]. Recent guidelines indicate that the β-D Glucan test would be more useful if targeted to subgroups of patients in which the clinical course or risk factors are particularly suggestive of invasive Candidiasis or other fungal infections. The test could identify IC cases from days to weeks before positivity of blood cultures, thus considerably reducing the median time for starting antifungal therapy [22]. In conclusion, the hypothesis proposed in this study will need to be confirmed in

larger prospective clinical trials. In fact, one of the limitations of our study is the small number of recruited patients which may have limited our ability to detect associations reported by other groups. Moreover, we lack molecular data on G6PD mutations. We defined G6PD− patients according to an enzyme activity <10%. Therefore, our cohort only includes patients harboring class I or II mutations that are likely to have the Mediterranean variant [6]. One could argue that our observations are not suitable for broad application because Sardinia is an area with a high prevalence of G6PD deficiency. However, G6PD deficiency is the most common enzyme defect in the world, affecting more than 400 million people and so it is not unlikely that our results may have an impact on routine practice in hematology departments [10].

Overall, our study is the first to report association between G6PD activity and susceptibility to IFD. The results obtained suggest that AML patients with chemotherapy-induced neutropenia and low levels of G6PD activity have a higher risk of developing IFD. Furthermore, we identified G6PD activity as a risk factor for *Candida* sepsis in patients with acute myeloid leukemia. Although studies on larger cohorts of patients are required, our findings could help clinicians identify patients at a higher risk of candidemia and thus allow for timely and targeted strategies for IFD prophylaxis and surveillance.

Acknowledgements

We are deeply grateful to the patients who participated in this study. We also wish to thank Anna Maria Koopmans for professional writing assistance.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at http://dx.doi.org/10.1080/10428194.2017.1312666.

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