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Changes in the incidence and mortality of candidemia in patients with hematological malignancies in the last ten years. SEIFEM 2015-B report

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Running title: Epidemiology of Candidemia in Hematological Malignancies

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The epidemiology of invasive fungal infections (IFI) among patients with hematological malignancies (HM) who are undergoing either conventional chemotherapy or hematopoietic stem cell transplantation (HSCT) is changing due to the introduction of new, effective antifungal agents for both prophylaxis and treatment that have markedly reduced aspergillosis or candidiasis [1-3].

In this retrospective multicenter study, we analyzed the incidence and mortality of candidemia among patients who were either undergoing chemotherapy because of various HM or HSCT (autologous or allogeneic). These results were compared with those observed in our two previous studies in the same categories of patients to verify any epidemiological changes [4,5].

This study was conducted between January 2011 and December 2015 in 23 hematology wards located throughout Italy that were participating in the SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine in Ematologia) consortium. Enrollment was limited to patients with acute myeloid or lymphoid leukemia (AML and ALL, respectively), non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM), excluding those patients who underwent HSCT who were analyzed separately. Due to the very low incidence of IFI, particularly candidemia, in our previous epidemiological studies [4], patients with Hodgkin's lymphoma, chronic leukemia and other chronic myeloproliferative disorders were excluded from this study. Recipients of either autologous HSCT (auto-HSCT) or allogeneic HSCT (allo-HSCT) were analyzed.

Each participating center completed a form, which included information on all patients who were admitted to the participating hematology departments and had developed a positive blood culture for *Candida spp*. during the study period. As a general rule, we collected information on all patients who had a diagnosis of the selected malignancies during the study period.

Mortality due to candidemia (attributable mortality-AM) was considered when patients died within 12 weeks after the onset of fever and had microbiological, histological or clinical evidence of active candidemia and when the responsible physician had excluded any alternative cause. AM

was calculated on the whole population of patients, while the case fatality rate was calculated on patients with candidemia.

Eighteen of the 23 hematological centers participating in the present study had also participated in the previous epidemiological SEIFEM studies on IFI in patients with HM and HSCT during the period between 1999-2003 [4,5]. The reported candidemia incidence and mortality rates during the two study periods were compared.

Statistical analyses were performed with the Intercooled Stata software, version 11, for Windows (Stata Corporation, College Station, TX).

During the study period, 16,529 patients with HM were admitted to the participating centers for conventional chemotherapy. The patients suffered from AML in 4,581 cases, ALL in 954 cases, either high- or low-malignancy NHL in 8,452 cases and MM in 2,542 cases. A total of 135 patients developed candidemia, and the overall incidence was 0.8%. In the different subsets of patients, the incidence ranged from 0.3% among patients with MM to 1.6% in patients with ALL. Among the 135 patients with candidemia, 63% of the infections occurred in patients with acute leukemia (52% in AML, 11% in ALL) (Table 1). The attributable mortality (AM) was 0.18% (30/16,259), ranging from 0% in ALL to 0.3% in AML. The case fatality rate in patients with candidemia was 22% (30/135), ranging from 0/15 (0%) in ALL to 6/8 (75%) in MM.

During the same observation period, 6,928 patients received an HSCT procedure; 4,338 patients underwent auto-HSCT; and 2,590 patients underwent allo-HSCT (Table 2). Overall, 59 patients developed candidemia with an incidence of 0.85%, 21 patients among the auto-HSCT recipients developed candidemia (0.48%), and 38 patients among the allo-HSCT recipients developed candidemia (1.5%) (Table 2). The AM for candidemia was 0.16% (11/6,928), 0.04% in auto-HSCT (2/4,338) and 0.34% (9/2,590) in allo-HSCT. The overall case fatality rate in patients

with candidemia was 18.6% (11/59); the overall case fatality rate was 9.5% (2/21) in auto-HSCT and 24% (9/38) in allo-HSCT.

In the first study, a total of 9,258 patients who received conventional chemotherapy were examined (3,012 AML, 1,173 ALL, 3,457 NHL, 1,616 MM), and in the second study, 3,228 transplanted patients (1,979 auto-HSCT and 1,249 allo-HSCT) were included (Tables 1-2). Although a statistically significant reduction in the incidence of candidemia was observed in the overall population over time (170/9,258 (1.8%) vs. 135/16,529 (0.8%); p-value <0.0001, CI 1.41-1.73), we could confirm this difference only in the subgroup of patients with AML (124/3,012 (4.1%) vs. 70/4,581 (1.5%); p-value <0.001, CI 1.46-1.82). No differences in the overall incidence of candidemia (30/3,228 (0.92%) vs. 59/6,928 (0.85); p-value 0.69) emerged in the recipients of HSCT, in the subgroup of auto-HSCT recipients (16/1,979 (0.8%) vs. 21/4,338 (0.48%); p-value 0.12) or in the subgroup of allo-HSCT recipients (14/1,249 (1.1%) vs. 38/2,590 (1.5%); p-value 0.38).

Regarding the AM, an overall significant reduction was observed in both patients treated with conventional chemotherapy (57/9,258 (0.6%) vs. 30/16,529 (0.18%); p-value <0.001, CI 157-2.13) and in patients treated using transplant procedures (15/3,228 (0.46%) vs. 11/6,928 (0.16%); p-value <0.004, CI 1.31-2.57). The AM in patients who were treated with conventional chemotherapy was influenced by the marked reduction of mortality among acute leukemia patients, both AML (44/3,012 (1.5%) vs. 14/4,581 (0.3%); p-value <0.001, CI 1.66-2.23) and ALL (8/1,173 (0.7%) vs. 0/954 (0%); p-value 0.01, CI 1.75-1.89); in contrast, no differences were observed in the groups of NHL and MM. Among the transplant population, a significantly lower mortality rate was observed only in recipients of auto-HSCT (7/1,979 (0.35%) vs. 2/4,338 (0.04%); p-value 0.002, CI 1.75-3.53).

The case fatality rate in patients with candidemia after conventional chemotherapy was significantly reduced in the present cohort compared to historical controls (57/170 (34%) vs. 30/135 (22%); p-value <0.03, CI 1.03-1.54). In particular, the case fatality rate results were significantly lower (44/124 (35%) vs. 14/70 (20%); p-value 0.02, CI 1.05-1.58) in both AML and ALL subgroups (8/22 (36%) vs. 0/15 (0%); p-value 0.008, CI 1.42-3.02). In contrast, no differences were detected in the NHL and MM subgroups (4/21 (19%) vs. 10/42 (24%); p-value 0.66, and 1/3 (33%) vs. 6/8 (75%); p-value 0.20, respectively).

The reduction of case fatality rates in transplant recipients was more significant for the overall (15/30 (50%) vs. 11/59 (18.6%); p-value 0.002, CI 1-39-4.20), for auto-HSCT (7/16 (44%) vs. 2/21 (9.5%); p-value 0.01, CI 1.27-4.59) and for allo-HSCT (8/14 (57%) vs. 9/38 (24%); p-value 0.02, CI 1.13-6.66).

For many years, candidemia represented one of the most relevant IFIs in HM patients, with a high mortality rate [6-8]. Recent reports showed that the incidence of candidemia is lower than in past years, probably because of the use of more effective prophylactic and/or therapeutic antifungal approaches [1-3].

Our epidemiological study compared two large multicenter cohorts of patients with HM who were treated with conventional chemotherapy or transplantation procedures during two different periods (before and after the introduction of the clinical practice of echinocandins and the azoles of the last generation, voriconazole and posaconazole). At present, we observed that the overall incidence of candidemia in the patients who were treated with conventional chemotherapy was significantly reduced, and it was markedly influenced by a relevant reduction of candidemia in AML patients. In contrast, in lymphoproliferative diseases, no differences were observed between the two observational periods. One potential explanation for this is that the cohort of AML patients who were treated between 1999-2003 had received fluconazole, itraconazole, or topical

polyenes as an antifungal prophylaxis, while a posaconazole prophylaxis was used in the majority (close to 90%) of AML patients who were on induction chemotherapy in our institutions since 2010. As reported, posaconazole contributed to reducing the incidence of mold infection and all invasive fungal infections compared to itraconazole/fluconazole in AML patients. Due to the low incidence of *Candida* infections in this study, little attention was dedicated to the prophylactic effect of the posaconazole prophylaxis on candidemia, while the main concern was on its marked efficacy against aspergillosis [9]. Nevertheless, posaconazole also seems to have the ability to prevent candidemia in patient populations who are undergoing transplant procedures. It is worth noting that in both the compared periods of the surveys, fluconazole was the most used drug for antifungal prophylaxis during neutropenia pre-engraftment, since posaconazole is indicated only for allo-HSCT with GVHD [10]. Indeed, the most recent IDSA guidelines extended the use of antifungal prophylaxis with posaconazole to all phases of allo-HSCT, so a significant reduction in the incidence of candidemia in recipients of allo-HSCT would be expected [11].

In the 2 cohorts of patients in the present study, the small number of deaths due to *Candida* observed in AML patients significantly influenced the overall AM. Conversely, there were no cases of attributable mortality observed among the 15 ALL patients with candidemia. This is important because no other reports so far have analyzed these data in a large HM population. Of interest, there were a very small number of patients with MM in both the study periods, but in the present study, 6/8 of the infected patients died because of candidemia. These data are not surprising because the use of empirical antifungal treatment is more frequent in AML and ALL subgroups than in MM or NHL groups. Furthermore, all of the deceased patients were in an unresponsive stage of their MM (refractory or multi-relapsed status), which may have compromised the ability of their immune systems to control the *Candida* infection. In addition, 3 of the patients died without receiving antifungals.

Finally, the following additional factors should be taken into account: a) the antifungal prophylaxis with posaconazole in AML may have contributed to reducing the incidence of candidemia in these patients; b) the use of more effective anti-yeast drugs, such as caspofungin, which resulted in echinocandin, were most frequently reported in the present study, in sharp contrast with our previous studies; c) liposomal amphotericin B was the most frequent polyene administered in the current study compared with a less than 10% administration rate in our previous study. We could hypothesize that all of these factors contributed in different ways to reducing the incidence of candidemia in patients with hematological malignancies in our recent study.

In conclusion, the present study shows that candidemia is currently a less relevant problem than it was in the past in HM patients, specifically in AML patients. Candidemia is still a concern in patients with lymphoproliferative malignancies where an antifungal prophylaxis is usually not given, and due to the introduction of new immune-modulating drugs (i.e., monoclonal antibodies, tyrosine kinase inhibitors), one would hypothesize a potential increase in the incidence of fungal infections, including candidemia.

DISCLOSURES

No disclosures are reported for this paper by any of the authors.

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Table 1. Incidence, attributable mortality (AM) and case fatality rate (CFR) among patients with hematological malignancies enrolled in 2 cohorts (historical cohorts and present study)

	Historical cohorts (1999-2003)				Present survey (2011-2015)				
	Patients	**Candidemia**	**AM**	**CFR**	**Patients**	**Candidemia**	**AM**	**CFR**	**p-value**
AML		124 (4.1%)				70 (1.5%)			<0.001
	3012		44 (1.5%)		4581		14 (0.3%)		<0.001
				44/124 (35%)				14/70 (20%)	0.02
ALL		22 (1.9%)				15 (1.6%)			0.60
	1173		8 (0.7%)		954		0 (0%)		0.01
				8/22 (36%)				0/15	0.008
NHL		21 (0.6%)				42 (0.5%)			0.45
	3457		4 (0.1%)		8452		10 (0.1%)		0.97
				4/21 (19%)				10/42 (24%)	0.66
MM		3 (0.2%)				8 (0.3%)			0.43
	1616		1 (0.06%)		2542		6 (0.2%)		0.18
				1/3 (33%)				6/8 (75%)	0.20
TOTAL		170 (1.8%)				135 (0.8%)			<0.001
	9258		57 (0.6%)		16529		30 (0.18%)		<0.001
				57/170 (34%)				30/135 (22%)	0.03

Legend: AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin's lymphoma; MM: multiple myeloma; AM: attributable mortality; CFR: case fatality rate

Table 2. Incidence, attributable mortality (AM) and case fatality rate (CFR) among patients who underwent transplant procedures (autologous and allogeneic) enrolled in 2 cohorts (historical and present study)

	Historical cohorts (1999-2003)				Present survey (2011-2015)				
	Patients	**Candidemia**	**AM**	**CFR**	**Patients**	**Candidemia**	**AM**	**CFR**	**p-value**
Auto-HSCT		16 (0.8%)				21 (0.48%)			0.12
	1979		7 (0.35%)		4338		2 (0.04%)		0.002
				7/16 (44%)				2/21 (9.5%)	0.01
Allo-HSCT		14 (1.1%)				38 (1.5%)			0.38
	1249		8 (0.64%)		2590		9 (0.34%)		0.20
				8/14 (57%)				9/38 (24%)	0.02
TOTAL		30 (0.92%)				59 (0.85%)			0.69
	3228		15 (0.46%)		6928		11 (0.16%)		0.004
				15/30 (50%)				11/59 (18.6%)	0.002

Legend: AM: attributable mortality; CFR: case fatality rate