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

The epidemiology of invasive fungal infections (IFI) among patients with hematologic malignancies 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 which have markedly reduced aspergillosis and 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 hematologic malignancies or HSCT (autologous or allogeneic). The 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 which were participating in the SEIFEM (*Sorveglianza Epidemiologica Infezioni Fungine in Ematologia* – Epidemiological Surveillance of Fungal Infections in Hematology) consortium. Enrollment was limited to patients with acute myeloid or lymphoid leukemia (AML and ALL, respectively), non-Hodgkin 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 lymphoma, chronic leukemia and other chronic myeloproliferative disorders were excluded from this study. Recipients of either autologous or allogeneic 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 was considered attributable to candidemia when patients died within 12 weeks of the onset of fever and had microbiological, histological or clinical evidence of active candidemia and when any alternative cause had been excluded. The attributable mortality rate was calculated on the whole population of patients, while the case fatality rate was calculated on patients with candidemia.

Eighteen of the 23 hematology centers participating in the present study had also participated in the previous SEIFEM epidemiological studies on IFI in patients with hematologic malignancies 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 Intercooled Stata software, version 11, for Windows (Stata Corporation, College Station, TX, USA).

During the study period, 16,529 patients with hematologic malignancies 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, for an overall incidence of 0.8%. The incidence in the different subsets of patients 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 rate 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 period of observation, 6,928 patients underwent HSCT (autologous in 4,338 patients and allogeneic in 2,590 patients) (Table 2). Of these patients, 59 developed candidemia, for an overall incidence of 0.85%: 21 of the autologous HSCT recipients developed candidemia (0.48%) and 38 of the allogeneic HSCT recipients developed candidemia (1.5%) (Table 2). The attributable mortality rate for candidemia was 0.16% (11/6,928), 0.04% in the autologous HSCT recipients (2/4,338) and 0.34% (9/2,590) in the allogeneic HSCT recipients. The overall case fatality rate in patients with candidemia was 18.6% (11/59); the case fatality rate was 9.5% (2/21) in autologous HSCT recipients and 24% (9/38) in those undergoing an allogeneic HSCT procedure.

In the first study, a total of 9,258 patients who received conventional chemotherapy were examined (3,012 with AML, 1,173 with ALL, 3,457 with NHL, and 1,616 with MM), while the second study included 3,228 transplanted patients (1,979 autologous HSCT recipients and 1,249 allogeneic HSCT recipients) (Tables 1 and 2). Although a statistically significant reduction in the incidence of candidemia was observed in the overall population over time [170/9,258 (1.8%) *versus* 135/16,529 (0.8%); $P<0.0001$; 95% confidence interval (CI): 1.41-1.73], we could confirm this difference only in the subgroup of patients with AML [124/3,012 (4.1%) *versus* 70/4,581 (1.5%); $P<0.001$; CI: 1.46-1.82]. No differences in the overall incidence of candidemia (30/3,228 (0.92%) *versus* 59/6,928 (0.85); $P=0.69$) emerged in the recipients of HSCT, in the subgroup of autologous HSCT recipients [16/1,979 (0.8%) *versus* 21/4,338 (0.48%); $P=0.12$] or in the subgroup of allogeneic HSCT recipients [14/1,249 (1.1%) *versus* 38/2,590 (1.5%); $P=0.38$].

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

The case fatality rate in patients with candidemia after conventional chemotherapy was significantly lower in the present cohort than in historical controls [57/170 (34%) *versus* 30/135 (22%); $P<0.03$; CI: 1.03-1.54]. In particular, the case fatality rates were significantly lower [44/124 (35%) *versus* 14/70 (20%); $P=0.02$; CI: 1.05-1.58] in both the AML and ALL subgroups [8/22 (36%) *versus* 0/15 (0%); $P=0.008$; CI: 1.42-3.02]. In contrast, no differences were detected in the NHL and MM subgroups

Table 1. Incidence, attributable mortality and case fatality rate among patients with hematologic malignancies enrolled in two 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	3012	124 (4.1%)	44 (1.5%)	44/124 (35%)	4581	70 (1.5%)	14 (0.3%)	14/70 (20%)	<0.001 <0.001 0.02
ALL	1173	22 (1.9%)	8 (0.7%)	8/22 (36%)	954	15 (1.6%)	0 (0%)	0/15	0.60 0.01 0.008
NHL	3457	21 (0.6%)	4 (0.1%)	4/21 (19%)	8452	42 (0.5%)	10 (0.1%)	10/42 (24%)	0.45 0.97 0.66
MM	1616	3 (0.2%)	1 (0.06%)	1/3 (33%)	2542	8 (0.3%)	6 (0.2%)	6/8 (75%)	0.43 0.18 0.20
TOTAL	9258	170 (1.8%)	57 (0.6%)	57/170 (34%)	16529	135 (0.8%)	30 (0.18%)	30/135 (22%)	<0.001 <0.001 0.03

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

[4/21 (19%) *versus* 10/42 (24%); *P*=0.66, and 1/3 (33%) *versus* 6/8 (75%); *P*=0.20, respectively].

The reduction of case fatality rates in transplant recipients was more significant for the overall group of recipients [15/30 (50%) *versus* 11/59 (18.6%); *P*=0.002; CI: 1-39-4.20], for autologous HSCT recipients [7/16 (44%) *versus* 2/21 (9.5%); *P*=0.01; CI: 1.27-4.59] and for allogeneic HSCT recipients [8/14 (57%) *versus* 9/38 (24%); *P*=0.02; CI: 1.13-6.66].

For many years, candidemia has been one of the most relevant IFI in patients with hematologic malignancies, with a high mortality rate.[6-8] Recent reports have shown 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 hematologic malignancies 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 latest-generation azoles, voriconazole and posaconazole). We observed that the overall incidence of candidemia in patients treated with conventional chemotherapy has decreased significantly, being markedly influenced by a relevant reduction of candidemia in AML patients. In contrast, among patients with lymphoproliferative diseases, no differences were observed between the two periods of observation. One potential explanation for this is that the cohort of AML patients who were treated between 1999-2003 received fluconazole, itraconazole, or topical polyenes as antifungal prophylaxis, whereas, since 2010, posaconazole prophylaxis has been used in the majority (close to 90%) of AML patients on induction chemotherapy in our institutions. As reported, posaconazole has contributed to reducing the incidences of mold infections and all IFI in AML patients compared to the incidences in corresponding patients treated with itraconazole/fluconazole.[9] Given the low incidence of *Candida* infections in that study, little attention was dedicated to the prophylactic effect of the posaconazole prophylaxis on candidemia, while the main focus was on its marked efficacy against aspergillosis.[9] Nevertheless, posaconazole also seems to have the ability to prevent candidemia in patients who are undergoing transplant procedures. It is worth noting that in both the compared periods of the surveys, fluconazole was the most widely used drug for antifungal prophylaxis during pre-engraftment neutropenia, since posaconazole was indicated only for allogeneic HSCT with graft-*versus*-host disease.[10] However, the most recent guidelines from the Infectious Diseases Society of America have extended the use of antifungal prophylaxis

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

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

AM: attributable mortality; CFR: case fatality rate.

with posaconazole to all phases of allogeneic HSCT, so a significant reduction in the incidence of candidemia in recipients of such transplants would be expected.[11]

In both cohorts in the present study the small number of deaths due to *Candida* observed in AML patients significantly influenced the overall attributable mortality. 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 such data in a large population of patients with hematologic malignancies. Of interest, there were very few patients with MM in both the study periods, but in the present study, 6/8 of the infected MM patients died because of candidemia. These data are not surprising because the use of empirical antifungal treatment is more frequent in patients with AML or ALL than in patients with MM or NHL. Furthermore, all of the patients with MM who died were in an unresponsive stage of their disease (refractory or multi-relapsed status), which may have compromised the ability of their immune systems to control the *Candida* infection. Furthermore, three of the patients died without receiving antifungal agents.

Finally, the following additional factors should be taken into account: (i) antifungal prophylaxis with posaconazole in AML may have contributed to reducing the incidence of candidemia in these patients; (ii) the use of more effective anti-yeast drugs, such as caspofungin, an echinocandin derivative, was more frequent in the present study, in sharp contrast with our previous studies; and (iii) liposomal amphotericin B was the most frequent polyene administered in the current study, whereas its rate of administration in our previous study was less than 10%. We could hypothesize that all of these factors contributed in different ways to reducing the incidence of candidemia in patients with hematologic 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 patients with hematologic malignancies, specifically in those with AML. Candidemia is still a concern in patients with lymphoproliferative malignancies, to whom antifungal prophylaxis is usually not given, in part because the introduction of new immune-modulating drugs (e.g., monoclonal antibodies, tyrosine kinase inhibitors) might increase the incidence of fungal infections, including candidemia.

Livio Pagano,[1] Giulia Dragonetti,[1] Chiara Cattaneo,[2] Francesco Marchesi,[3] Barbara Veggia,[4] Alessandro Busca,[5] Anna Candoni,[6] Lucia Prezioso,[7] Marianna Criscuolo,[1] Simone Cesaro,[8] Mario Delia,[9] Rosa Fanci,[10] Marta Stanzani,[11] Antonella Ferrari,[12] Bruno Martino,[13] Lorella Melillo,[14] Gianpaolo Nadali,[15] Edoardo Simonetti,[16] Stelvio Ballanti,[16] Marco Picardi,[17] Carlo Castagnola,[18] Nunzia Decembrino,[19] Marco Gazzola,[20] Nicola Stefano Fracchiolla,[21] Valentina Mancini,[22] Annamaria Nosari,[22] Maria Ilaria Del Principe,[23] Franco Aversa[7] and Mario Tumbarello[24] on behalf of the SEIFEM group (Sorveglianza Epidemiologica Infezioni Fungine in Ematologia)

[1]Department of Onco-Hematology, Fondazione Policlinico Universitario A. Gemelli-Università Cattolica del Sacro Cuore, Rome; [2]Hematology, Spedali Civili, Brescia; [3]Hematology and Stem Cell Transplant Unit Regina Elena National Cancer Institute, Rome; [4]Hematology, Azienda Ospedaliera S.Giovanni Addolorata, Rome; [5]SSD Trapianto Cellule Staminali, A.O.U. Citta' della Salute, Torino; [6]Clinica Ematologica, Centro Trapianti e Terapie Cellulari, Azienda Sanitaria Universitaria Integrata di Udine; [7]Hematology, University of Parma; [8]Pediatric Hematology Oncology, Azienda Ospedaliera Universitaria Integrata Verona; [9]Dipartimento dell'Emergenza e dei Trapianti Di Organo - U.O Ematologia con Trapianto - Azienda Ospedaliero-Universitaria - Policlinico di Bari; [10]Hematology, University of Firenze; [11]Hematology, University of Bologna; [12]UOC Ematologia, Az. Ospedaliera Sant'Andrea, Università "Sapienza" Rome; [13]Hematology, Bianchi Melacrino Morelli Hospital, Reggio Calabria; [14]Hematology, S.Giovanni Rotondo Hospital; [15]Hematology, University of Verona; [16]Hematology, University of Perugia; [17]Department of Advanced Biomedical Science, Federico II University, Naples; [18]Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia; [19]Pediatric Onco-Hematology, University of Pavia; [20]Hematology and Clinical Immunology, Padova; [21]Hematology

Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milano [22]Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milano; [23]Hematology, Dipartimento di Biomedicina e Prevenzione Università degli Studi di Roma Tor Vergata, Rome and [24]Institute of Infectious Diseases, Fondazione Policlinico Universitario A. Gemelli- Università Cattolica del Sacro Cuore, Rome, Italy.

Correspondence: livio.pagano@unicatt.it
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References

1. Caira M, Candoni A, Verga L, et al. Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study). Haematologica. 2015;100(2):284-292.
2. Dragonetti G, Criscuolo M, Fianchi L, Pagano L. Invasive aspergillosis in acute myeloid leukemia: are we making progress in reducing mortality?. Med Mycol. 2017;55(1):82-86.
3. Cornely OA, Gachot B, Akan H, et al. Epidemiology and outcome of fungemia in a cancer cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). Clin Infect Dis. 2015;61(3):324-331.
4. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 2006;91(8):1068-1075.
5. Pagano L, Caira M, Nosari A, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clin Infect Dis. 2007;45(9):1161-1170.
6. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis. 1999;28(5):1071-1079.
7. Pagano L, Antinori A, Ammassari A, et al. Retrospective study of candidemia in patients with hematological malignancies. Clinical features, risk factors and outcome of 76 episodes. Eur J Haematol. 1999;63(2):77-85.
8. Okinaka K. Candidemia in cancer patients: focus mainly on hematological malignancyand hematopoietic stem cell transplantation. Med Mycol J. 2016;57(3):J117-123.
9. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348-359.
10. Maertens J, Marchetti O, Herbrecht R, et al. Third European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. Bone Marrow Transplant. 2011;46(5):709-718.
11. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1-e60.