MAJOR ARTICLE

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)

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Background. Anti-cancer treatment and the cancer population have evolved since the last European Organisation for Research and Treatment of Cancer (EORTC) fungemia survey, and there are few recent large epidemiological studies.

Methods. This was a prospective cohort study including 145 030 admissions of patients with cancer from 13 EORTC centers. Incidence, clinical characteristics, and outcome of fungemia were analyzed.

Results. Fungemia occurred in 333 (0.23%; 95% confidence interval [CI], .21–.26) patients, ranging from 0.15% in patients with solid tumors to 1.55% in hematopoietic stem cell transplantation recipients. In 297 evaluable patients age ranged from 17 to 88 years (median 56 years), 144 (48%) patients were female, 165 (56%) had solid tumors, and 140 (47%) had hematological malignancies. Fungemia including polymicrobial infection was due to: *Candida* spp. in 267 (90%), *C. albicans* in 128 (48%), and other *Candida* spp. in 145 (54%) patients. Favorable overall response was achieved in 113 (46.5%) patients by week 2. After 4 weeks, the survival rate was 64% (95% CI, 59%–70%) and was not significantly different between *Candida* spp. Multivariable logistic regression identified baseline septic shock (odds ratio [OR] 3.04, 95% CI, 1.22–7.58) and tachypnoea as poor prognostic factors (OR 2.95, 95% CI, 1.66–5.24), while antifungal prophylaxis prior to fungemia (OR 0.20, 95% CI, .06–.62) and remission of underlying cancer (OR, 0.18; 95% CI, .06–.50) were protective.

Conclusions. Fungemia, mostly due to *Candida* spp., was rare in cancer patients from EORTC centers but was associated with substantial mortality. Antifungal prophylaxis and remission of cancer predicted better survival.

Keywords. candida; candidemia; cancer; leukemia.

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Candidemia occurs frequently, is a severe clinical complication, and is associated with high morbidity and mortality, particularly in patients being treated for cancer [1–3]. Yet the epidemiology of fungemia in these patients has not been fully elucidated [4].

In the 1990s the European Organisation for Research and Treatment of Cancer (EORTC) conducted a study of fungemia in patients undergoing treatment of solid tumors or hematological cancers [5]. Of 270 episodes, 92% were caused by *Candida* spp., and key results

showed an association of *Candida glabrata* infection, advanced age, and disease severity with mortality. Since then epidemiology may have changed for several reasons: A changing distribution of *Candida* species has been reported [6], additional antifungal drugs have become available, particularly the echinocandin class [7, 8], indications for immunosuppressive therapy, and for hematopoietic stem cell transplantation (HSCT) in particular have increased [9], and early antifungal treatment including prophylaxis has been adopted [10–12].

We have conducted a second study of the epidemiology of fungemia in cancer. Objectives of this study were to determine fungal pathogen distribution, prognostic factors for outcome, and crude and attributable mortality. An additional aim of this study was to describe the incidence of fungemia in relation to the number of hospital admissions of adult cancer patients in Europe.

MATERIAL AND METHODS

This intergroup study was sponsored by the EORTC (protocol 65031) and conducted in collaboration with the Infectious Disease Working Party of the German Society for Hematology and Oncology and the Infectious Disease Working Party of the European Group for Blood and Marrow Transplantation. Centers affiliated with these Infectious Diseases Groups were invited to participate.

The protocol was approved by the ethics committees and institutional review boards of the participating centers. Two groups of patients were selected. Group A comprised all admissions to the participating wards of patients ≥18 years of age with a diagnosis of a solid tumor, hematological malignancy, and/or recipients of any type of HSCT. Admission was defined as ≥1 night's in-hospital stay. Group B, a subgroup of group A, included all patients who had a fungus isolated from ≥1 blood culture and for whom there was signed informed consent. Once the eligibility criteria were fulfilled, patients from group B were prospectively registered at the EORTC Data Center by telephone or web access. Patients could only be registered once. Case report forms were completed either in paper form or by electronic remote data capture. For this epidemiologic study approximately 300 fungemia patients were expected over a study period of 2 years. As this was a noninterventional study, no randomization or stratification was done. and no adverse events were to be reported.

Fungal isolates were sent to the EORTC-IDG Mycology Reference Laboratory for Yeasts, Institute of Microbiology, Lausanne University Hospital, Lausanne, Switzerland for purity check, and confirmation of identification, which overruled identification done by the study sites. Only *Candida* isolates were tested for their susceptibility to fluconazole, voriconazole, posaconazole, amphotericin B by EUCAST, and caspofungin by the CLSI method.

Criteria evaluated for group A were reporting period (date of first patient in to date of last patient out), number of admissions of patients with a diagnosis of malignant disease or HSCT, type of transplantation, number of admissions of patients by type of solid tumor or hematological malignancy during the reporting period and number of admissions of patients with a documented fungemia by underlying disease type. These summary data were collected at regular time intervals during the reporting period. Additional information collected for group B patients were demographics, details of malignant disease and predisposing factors for the development of fungemia, such as previous surgery, radiotherapy, antibiotics, total parenteral nutrition, major organ dysfunction, presence of neutropenia, antifungal prophylaxis and treatment, date of diagnosis of fungemia, number and source of positive blood cultures, clinical signs and symptoms of fungemia, and organ involvement.

Group B patients were followed up to 12 weeks from diagnosis of fungemia, and data were collected on antifungal treatment, clinical and microbiological response, and survival. Treatment was considered adequate when the isolate was susceptible to the initial treatment. Response to treatment was determined at weeks 2, 4, and 12. Clinical evaluation of response was categorized as follows: Complete response (complete resolution of clinical signs and symptoms of fungemia), partial response (significant but incomplete resolution of clinical signs and symptoms), stable disease (no significant improvement in clinical signs and symptoms), and progressive disease (worsening of clinical signs and symptoms). Microbiological evaluation of response was categorized as complete microbiological response (3 consecutive negative blood cultures), no microbiological response (persistently positive blood cultures), and microbiological relapse (complete microbiological response followed by a positive blood culture within the 12 week follow-up). If no follow-up blood cultures were obtained, microbiological response was categorized as not assessable. Global response was defined as complete or partial clinical response with complete microbiological response.

Survival data were graphically presented by Kaplan–Meier curves and compared by using log rank test. We considered 2 binary outcomes: death within 4 weeks, and favorable overall response at 2 weeks. Differences in categorical variables were assessed with χ^2 and Fisher exact tests, differences in continuous variables were assessed with t-test and Mann–Whitney test. Multivariable logistic regression models were built with stepwise variable selection. All statistical analyses were done with SAS 9.3 (SAS Institute Inc., Cary, North Carolina).

Explanatory variables considered for the outcomes of "favorable overall response at 2 weeks" and "death within 4 weeks" were: age, gender, underlying disease and its status, time interval between hospital admission to onset of fungemia, HSCT, treatment given within 30 days before diagnosis (chemotherapy,

radiation therapy, immunosuppressive drugs, major surgical procedure, total parenteral nutrition, antibacterials, antifungals), neutropenia, colonization at baseline, signs and symptoms, organ involvement, catheter correlation (whether after removal of the central venous catheter the same pathogen was found as previously isolated in blood culture), and the pathogen.

RESULTS

From 1 January 2005 to 2 November 2009, a total of 145 030 cancer patients were admitted to 13 participating centers in 8 countries. Fungemia was diagnosed in 333 of these patients. The overall incidence rate was 0.23%, ranging from 0.15% in solid tumor patients to 1.55% in HSCT recipients. Incidence rates according to underlying malignancy are listed in Table 1. We excluded 36 patients for whom no detailed data were obtained, mostly because they did not provide informed consent. Of the remaining 297 patients with fungemia (Group B), 165 (56%) had a solid tumor, 140 (47%) patients had a hematological malignancy, and 50 (17%) underwent HSCT. Baseline characteristics including potential risk factors for fungemia are detailed in Table 2.

General signs and symptoms at diagnosis of fungemia were fever >37°C (98.6°F) in 93% (275/297), ≥38°C (100.4°F) in 76% (225/297), septic shock in 10% (30/297), tachycardia in 70% (204/292), tachypnoea in 33% (95/290), myalgia in 20% (53/271), and chills in 30% (88/293) of the patients.

At baseline, organ involvement was evaluated in 265 (89%) patients, whereas data were missing for 32 (11%) patients. Organs were involved in 83 of 265 (31%) patients. These were skin in 13 (5%), liver/spleen in 12 (5%), kidney/urinary tract in 10 (4%), other intraabdominal involvement in 9 (3%), endocardium in 6 (2%), eye in 6 (2%), vascular in 3 (1%), and central nervous system (CNS) in 2 (<1%) patients. Organ involvement decreased from 31% (83/265) at baseline to 16% (9/55) in week 12.

Of 251 (85%) patients with central vascular device the catheter was retained in 84 (33%), whereas it was removed in 167 (67%) patients, a median of 3 days after diagnosis of fungemia (range, 0–112 days). Removed catheters were cultured in 91% (152/167) of patients. Of 152 catheter cultures, 69 (45%) showed fungal growth. In 67 (97%) of them the same fungal species as in the initial blood culture was found.

Fungemia was caused by a single pathogen in 288 (97%) patients, 9 (3%) patients had infections due to more than 1 species, resulting in a total of 306 isolates. Pathogens are listed according to underlying diseases and HSCT in Table 3. *Candida* species accounted for 274 (90%) isolates. Central review of fungal pathogens was offered to all centers except the reference center itself (35 isolates), for which correct identification was taken for granted. Of the remaining 271 pathogens, central reviews for 172 (63%) were available. Isolate identification by the sites was confirmed by the reference laboratory in 164 (95%) cases. Misidentified isolates were found in 8 cases, and these were evenly distributed across study sites; details are given in Table 3. Full susceptibility tests were done for 141 isolates of *Candida* spp. All 63 *C. albicans* and 17 *C. parapsilosis* isolates were susceptible to all antifungals. Of 27 *C. tropicalis* all but 2 strains were susceptible to all the antifungals, whereas the 2 remaining strains were only susceptible to posaconazole and amphotericin B. EUCAST deems that there is insufficient evidence to consider *C. glabrata* and *C. krusei* as good targets for treatment with

Table 1. Fungemia Incidence Rates by Underlying Malignancy (Fungemia Patients per Admissions)

Patient Group	Incidence [% (95% CI)]	Patients With Fungemia per Observed Group; N/N
Overall	**0.23% (.21–.26)**	**333/145 030**
Solid tumor without HSCT	**0.15% (.13–.18)**	**174/114 811**
Gastro-intestinal	0.37% (.30–.46)	88/23 718
Lung	0.05% (.01–.11)	5/10 976
Breast	0.05% (.02–.10)	8/16 137
Genito-urinary	0.20% (.14–.27)	42/21 389
Head and Neck	0.13% (.08–.20)	24/18 248
Other	0.03% (.01–.06)	7/24 343
Solid tumor with HSCT	**1.55% (.19–5.49)**	**2/129**
Allogeneic HSCT		1/5
Autologous HSCT	0.81% (.02–4.41)	1/124
Hematological malignancies without HSCT	**0.42% (.35–.50)**	**114/27 195**
ALL	0.64% (.38–1.01)	18/2801
AML	0.89% (.63–1.21)	39/4403
CLL	0.29% (.09–.67)	5/1738
CML	0.37% (.04–1.32)	2/543
MDS	0.57% (.19–1.33)	5/875
Lymphoma	0.29% (.21–.40)	38/12 933
Multiple myeloma	0.15% (.05–.35)	5/3356
Other	0.37% (.04–1.32)	2/546
Hematological malignancies with HSCT	**1.46% (1.06–1.97)**	**42/2871**
Allogeneic HSCT – related donor	2.10% (1.18–3.44)	15/715
Allogeneic HSCT – unrelated donor	1.99% (1.00–3.54)	11/552
Autologous HSCT	1.00% (.57–1.61)	16/1604
HSCT without associated malignancies		**1/24**

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome.

Table 2. Baseline Characteristics of European Patients With Cancer and Fungemia (N = 297)

Characteristic	Value N/N
Age, median (min – max)	56 (17–88)
Sex, male	153/297 (52%)
Days from hospital admission to diagnosis of fungemia, mean ± std	23 ± 21
Neutropenia <500 cells/μL at time of diagnosis of fungemia	110/286 (38%)
Vascular access device upon fungemia diagnosis	280/297 (94%)
Central venous catheter	238/297 (80%)
Peripheral catheter	29/297 (10%)
Both	13/297 (4%)
Underlying disease	
Solid Tumor[a]	165/297 (56%)
Gastro-intestinal	74/165 (45%)
Lung	6/165 (4%)
Breast	9/165 (5%)
Genito-urinary	41/165 (25%)
Head and neck	23/165 (14%)
Other	11/165 (7%)
Unknown	1/165 (0.6%)
Hematological[a]	140/297 (47%)
Acute lymphoblastic leukemia	23/140 (16%)
Acute myelogenous leukemia or myelodysplastic syndrome	60/140 (43%)
Lymphoma incl. chronic lymphocytic leukemia	44/140 (31%)
Other	13/140 (9%)
HSCT without associated malignancy	1/297 (0.3%)
Status of malignancy	
Solid Tumor[a]	
At diagnosis	29/165 (18%)
Complete or partial remission	29/165 (18%)
No change or progressive disease	107/165 (65%)
Hematological malignancy[a]	
Onset	19/140 (14%)
Complete remission	20/140 (14%)
Partial remission, bone marrow hypoplasia, refractory, or relapse	101/140 (72%)
Treatment at fungemia diagnosis	
HSCT	50/297 (17%)
Allogeneic HSCT	28/297 (9%)
Autologous HSCT	22/297 (7%)
Chemotherapy[b]	142/296 (48%)
Radiation therapy[b]	22/296 (7%)
Immunosuppressive drugs[b]	88/293 (30%)
Major surgical procedure[b]	69/297 (23%)
Total parenteral nutrition[b]	118/295 (40%)
Stopped prior to fungemia diagnosis	36/295 (12%)
On-going at fungemia diagnosis	82/295 (28%)
Antibiotics[b]	255/297 (86%)
Antifungals[b]	89/297 (30%)
Prophylactic	32/297 (11%)
Empiric or curative	57/297 (19%)

Abbreviation: HSCT, hematopoietic stem cell transplantation.

[a] 9 patients had both a solid tumor and a hematological malignancy.

[b] Within 30 days prior to diagnosis of current fungemia episode.

azole antifungals. The 19 *C. glabrata* and all 15 *C. krusei* were susceptible to amphotericin B, but 3 *C. glabrata* and 5 *C. krusei* were resistant to caspofungin.

The median time from blood culture sampling to initiation of antifungal treatment was 2 days, with a minimum of 0 and a maximum of 21 days. A total of 242 (81%) patients received treatment for fungemia, and 228 started with antifungal treatment within the first week. Of these 6 (3%) received antifungal combination therapy, 53 (23%) received >1 antifungal sequentially in the first week, and 169 (74%) received a single antifungal: 32 (14%) intravenous amphotericin B, 51 (22%) echinocandin, 79 (35%) fluconazole, 6 (3%) voriconazole, and 1 (0.4%) other. Only 14 of 228 (6%) patients receiving initial intravenous treatment were switched to an oral antifungal within the first week after diagnosis. The pathogens cultured fell within the spectrum of the antifungals chosen for treatment in 226 of 297 (76%) cases. Overtly incorrect treatment decisions, such as initiating an antifungal despite known resistance, were infrequent. Overall, 55 (19%) patients did not receive antifungal treatment, and 14 patients received treatment more than 7 days post diagnosis of fungemia. No antifungal treatment at all was given to 27 of 118 (23%) patients with *C. albicans* fungemia and to 20 of 140 (14%) patients with candidemia due to other species ($P = .08$).

Breakthrough fungemia, defined as patients being treated for ≥1 day before the first positive blood culture was drawn, occurred in 69 (23%) patients. Most of these infections were caused by a single species; 2 were due to more than 1 species. Breakthrough candidemia was due to: *C. albicans* (14; 20%) and *Candida* other than *C. albicans* (38; 55%), namely *C. krusei* (15; 22%), *C. glabrata* (5; 7%), *C. tropicalis* (6; 9%), *C. parapsilosis* (5; 7%), *C. norvegensis* (2; 3%), *C. dubliniensis* (1; 1%), *C. kefyr* (2; 3%), and *Candida* spp. (2; 3%). Two infections were caused by more than 1 species: *C. albicans* & *C. glabrata* and *C. albicans* and *C. parapsilosis*. In 10 (14%) patients breakthrough pathogens were noncandida yeast: *Trichosporon* spp. (5; 7%), *Saprochaete capitata* (formerly *Geotrichum capitatum*) (2; 3%), *S. clavata* (1; 1%), *Cryptococcus laurentii* (1; 1%), and *Saccharomyces* sp. (1; 1%). Other positive blood cultures classified as breakthrough infections grew molds in 1 patient each: *Fusarium* sp., *Syncephalastrum racemosum*, *Rhizopus oryzae,*

Table 3. Fungi[a] Isolated From Blood Cultures in European Patients With Cancer, by Underlying Disease and Treatment Groups (N = 297)

Pathogen Isolated by Treating Center	Total n = 297 (%)	Solid Tumor[b] n = 165 (%)	Hematological Malignancy[b] n = 140 (%)	Allogeneic HSCT n = 28 (%)	Autologous HSCT n = 22 (%)	No Transplant n = 247 (%)
Single pathogen	**288 (97.0%)**	**159 (97%)**	**137 (98%)**	**27 (96.4%)**	**22 (100%)**	**239 (96.8%)**
Candida albicans	120 (40.4%)	92 (56%)	31 (22%)	2 (7.1%)	7 (31.8%)	111 (44.9%)
Non-albicans candida	138 (46.5%)	59 (36%)	82 (59%)	21 (75.0%)	12 (54.6%)	105 (42.5%)
C. glabrata	29 (9.8%)	25 (15.2%)	6 (4.3%)	1 (3.6%)	1 (4.5%)	27 (10.9%)
C. tropicalis	39 (13.1%)	11 (6.7%)	30 (21.4%)	2 (7.1%)	4 (18.2%)	33 (13.3%)
C. parapsilosis	28 (9.4%)	16 (9.7%)	11 (7.9%)	5 (17.9%)	2 (9.1%)	21 (8.5%)
C. krusei	25 (8.4%)	5 (3.0%)	20 (14.3%)	6 (21.4%)	4 (18.2%)	15 (6.1%)
C. kefyr	7 (2.4%)	1 (<1%)	6 (4.3%)	2 (7.1%)	1 (4.5%)	4 (1.6%)
C. norvegensis	3 (1.0%)	. . .	3 (2.1%)	1 (3.6%)	. . .	2 (0.8%)
C. dubliniensis	2 (<1%)	. . .	2 (1.4%)	1 (3.6%)	. . .	1 (0.4%)
C. guilliermondii	2 (<1%)	1 (<1%)	1 (<1%)	1 (3.6%)	. . .	1 (0.4%)
C. rugosa	1 (<1%)	. . .	1 (<1%)	. . .	. . .	1 (0.4%)
Other Candida[c]	2 (<1%)	. . .	2 (1.4%)	2 (7.1%)	. . .	. . .
Non-candida yeast[d]	17 (5.7%)	5 (3%)	13 (9%)	2 (7.1%)	2 (9.1%)	13 (5.3%)
Cryptococcus sp.	4 (1.3%)	1 (<1%)	3 (2%)	. . .	. . .	4 (1.6%)
Mold, NOS[e]	7 (2.4%)	1 (<1%)	7 (5%)	2 (7.1%)	1 (4.6%)	4 (1.6%)
Trichoderma longibrachiatum	2 (<1%)	1 (<1%)	1 (<1%)	. . .	. . .	2 (<1%)
Two pathogens isolated	**9 (3%)**	**6 (3%)**	**3 (2%)**	**1 (3.6%)**	. . .	**8 (3.2%)**
Candida albicans and non-albicans candida[f]	6 (2.0%)	4 (2.4%)	2 (1.4%)	. . .	. . .	6 (2.4%)
Candida albicans and non-candida yeast[g]	2 (<1%)	2 (1.2%)	. . .	. . .	. . .	2 (<1%)
Non-albicans candida[h]	1 (<1%)	. . .	1 (<1%)	1 (3.6%)	. . .	. . .

Abbreviations: HSCT, hematopoietic stem cell transplantation; NOS, not otherwise specified.

[a] Identified by local laboratory.

[b] 9 had both, a solid tumor and a hematological malignancy.

[c] 2 NOS.

[d] 8 *Trichosporon* spp., 4 *Saprochaete capitata*, 1 *S. clavata*, 2 *Saccharomyces* spp., 1 *S. cerevisiae*, 1 NOS.

[e] 3 *Fusarium* spp., 1 *Rhizopus oryzae*, 1 *Syncephalastrum racemosum*, 1 *Paecilomyces* sp., 1 NOS.

[f] 4 *C. glabrata*, 2 *C. parapsilosis*.

[g] 2 NOS.

[h] 1 *C. norvegensis*, 1 *C. inconspicua*. The following isolates were reclassified by the central laboratory: *C. albicans* → *C. dubliniensis*, *C. glabrata* → *C. krusei*, *C. rugosa* → *G. capitatum*, *C. dubliniensis* → *C. albicans*, *C. albicans* → *C. parapsilosis*, *C. albicans* → *C. tropicalis*, *C. krusei* → *C. parapsilosis*, *Trichosporon asahii* → *C. tropicalis*. For mold infections other than fusariosis this study could not rule out contamination rather than blood stream infection.

and *Paecilomyces* species. Breakthrough fungemia was treated in 57 (83%) patients, while 12 (17%) received no antifungal drugs. The median time to new antifungal treatment was 2 days (range 0 to 21 days).

Global response was achieved in 87 (36%) and 26 (11%) evaluable patients by week 2. Seven (6%) patients had a microbiological relapse, which occurred between day 29 and day 62. At week 2, treatment response was not assessed in 46 (15%) patients, and 8 (3%) patients were lost to follow-up. Of the remaining 243 patients, 69 (28%) had died and thus were regarded as treatment failures, and 61 (25%) patients had either failed treatment or fungemia had relapsed. In total, treatment failure was observed in 130 of 243 (53.5%) evaluable patients. In a multivariable logistic regression model baseline characteristics predicting a higher risk of failure were tachycardia (odds ratio [OR] 2.07, 95% confidence interval [CI], 1.10–3.92, $P = .03$), myalgia (OR 2.37, 95% CI, 1.13–4.98, $P = .02$), and septic shock (OR 3.57, 95% CI, 1.30–9.80, $P = .01$).

Overall mortality was 35% and 49% at weeks 4 and 12 (Figure 1). For patients who had achieved clinical complete response, partial response, or stable disease 2 weeks after diagnosis of fungemia the crude week 4 survival rate was 86%. In contrast, 4 week survival in patients with progressive fungal disease was 58% ($P < .001$).

Investigators attributed 50 (72%) of the deaths within the first 2 weeks to fungemia. Survival rates did not differ between

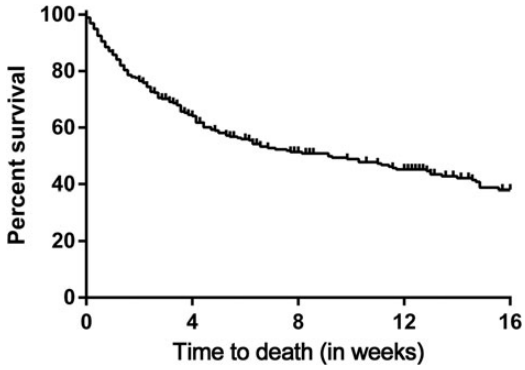

Figure 1. Overall survival in 297 European cancer patients with fungemia.

patient groups with fungemia due to *C. albicans*, non-albicans *Candida* and noncandida yeasts. When comparing survival rates for fungemia caused by the most frequent *Candida* spp., no difference was found between *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* (Figure 2).

For 33 (11%) patients follow-up was less than 1 month, so that 264 (89%) patients underwent analysis of baseline factors potentially prognostic for 28-day survival. Multivariable logistic regression identified presence of septic shock (OR 3.04, 95% CI, 1.22–7.58) and tachypnoea as negative prognostic factors (OR 2.95, 95% CI, 1.66–5.24). Positive prognostic factors were remission of underlying malignancy (OR 0.18, 95% CI, .06–.50) and antifungal prophylaxis at any time within 30 days prior to diagnosis of fungemia (OR 0.20, 95% CI, .06–.62). Median time to central venous catheter removal was 3 days and removal vs no removal had no impact on 28-day survival. Comparing patients with deep seated organ involvement (CNS, eye, heart/endocarditis, kidney/urinary tract infection, liver/spleen, skin) and patients without documented organ involvement, risk of death at day 28 did not differ.

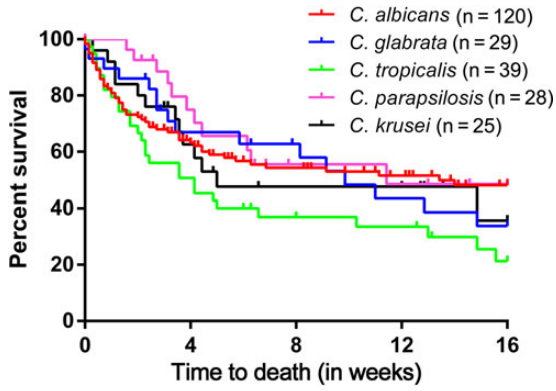

Figure 2. Species-specific survival in 275 European cancer patients with candidemia (*P* value .14, overall test).

DISCUSSION

In a large multinational study in cancer patients the overall incidence of fungemia was 0.23% and ranged from 0.15% in solid tumor patients to 1.55% in HSCT recipients [13]. In gastrointestinal cancer, fungemia rates were comparably higher than with other tumors, which reflects abdominal surgery as a risk factor for invasive candidiasis [14].

An epidemiological shift from *C. albicans* to other *Candida* spp. is an ongoing discussion, but published data are inconsistent, probably reflecting local epidemiology, rather than global trends [15, 16]. The proportion of *C. albicans* among candidemias (47%) was similar to the previous EORTC study (49%) [5]. In both studies non-albicans *Candida* species were more frequent in hematological disease than with solid tumors [5]. One potential explanation is higher selection pressure due to more extensive antifungal exposure in hematology [17]. Molds other than *Fusarium* spp. isolated from blood cultures technically fulfil the definition of fungemia, but contamination cannot be excluded, if isolated only from a single blood culture [18]. A limitation of our noninterventional study is the absence of a standardized evaluation of organ involvement, which may have been underestimated.

Contrary to the overall species distribution, pathogens found in breakthrough fungemia were *C. albicans* in 20% only. A recent overview of >100 clinical trials evaluating antifungal prophylaxis found similar results, likely because *C. albicans* is effectively treated by the systemically active antifungals used in these trials as well as in our study [19, 20]. Another finding of our study is the continuing low resistance rate of *C. albicans* in this population, despite high azole usage. This has been described previously in a longitudinal evaluation during long-term azole exposure [19].

Central catheters were removed after a median of 3 days, reflecting a median of 2 days from obtaining blood cultures to observing fungal growth. Current guidelines recommend removing any indwelling lines once fungemia is diagnosed because of likely biofilm formation [21–23]. But central venous devices present at onset of fungemia were retained in a third of patients, and 19% of all fungemia patients did not receive any antifungal treatment. These remarkable findings may be explained by our broad enrolment criteria including patients with minimized treatment interventions in palliative settings. Treatment response in our study was lower than in recent large randomized clinical trials, again emphasizing healthier patient populations in phase 3 trials [24–26]. Mortality rates were comparably higher in our study, but mortality did not correlate with fungal species, although in the previous EORTC study

C. glabrata was associated with worse outcome [5]. Both antifungal prophylaxis and remission of malignant disease independently protected from adverse outcome. Between the 2 study periods, antifungal management underwent major developments, such as the introduction and more widespread use of broad spectrum antifungals, which are now frequently used. It is also encouraging that fungal species were correctly identified on-site in the vast majority of cases.

This epidemiological study covers the years 2005–2009. Whether all findings are applicable to 2015 is not clear, and epidemiological developments need continuous observation.

In summary, we have defined the fungemia rate in patients with cancer for the first time and described recent changes in prognostic factors [17, 21, 23].

Notes

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APPENDIX

List of where and when the study has been presented in part elsewhere, if applicable:

ECCMID 2012 in London: Cornely, O.A., Gachot, B., Akan, H. Bassetti, M., Uzun, O., Kibbler, C. C., Marchetti, O., Bille, J., de Burghgraeve, P., Pylkkanen, L., Ameye, L., Paesmans, M., and Donnelly, P. J. Epidemiology and mortality of fungaemia in cancer patients—a clinical cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031), CMI:18 Suppl s3;9 (O109).