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Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy^{☆,☆☆,★,★★}

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Abstract

This is a retrospective, single-center study of adult patients with newly diagnosed acute myelogenous leukemia (AML), who received intensive induction timed sequential chemotherapy from 1/2005 to 6/2010. Among 254 consecutive AML patients, 123 (48.4%) developed an invasive fungal infection (IFI): 14 (5.5%) patients with invasive candidiasis (IC) and 108 (42.5%) patients with invasive mould infections (IMI). Among 108 IMI identified, 4 (3.7%) were proven, 1 (0.9%) probable, and 103 (95.4%) were possible, using current definitions. Overall, 6-month mortality was 23.7% (27/114) and 20.6% (26/126) for patients with and without an IFI, respectively. Older age (> 50 years; hazard ratio [HR]: 2.5, $P < 0.001$), female gender (HR: 1.7, $P = 0.006$), and baseline renal and/or liver dysfunction (HR: 2.4, $P < 0.001$) were the strongest mortality predictors. We report relatively low rates of IC despite lack of routine primary antifungal prophylaxis, albeit associated with poor long-term survival. High rates of IMI, the vast majority with a possible diagnosis, were observed. Host-related variables (demographics and baseline organ dysfunction) were identified as the most significant risk factors for IFI and mortality predictors in this series.

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Keywords

Invasive fungal infections; Acute myeloid leukemia; Epidemiology; Risk factors; Survival

1. Introduction

The incidence of invasive fungal infections (IFI) in patients with acute leukemia and other hematologic malignancies has ranged between 2% and 49%, with reported mortality up to 60% (Auberger et al., 2008; Bow et al., 1995; Cordonnier et al., 2009; Cornely et al., 2007; Hahn-Ast et al., 2010; Hammond et al., 2010; Malagola et al., 2008; Rotstein et al., 1999; Vehreschild et al., 2007, 2010; Winston et al., 1993). Variability in incidence rates can be attributed, in part, to patient population selection, chemotherapy regimens, and variable patterns of systemic antifungal prophylaxis administration. Host (older age, type and disease status of hematologic malignancy, duration of neutropenia, candidal colonization) and treatment (cytotoxic regimens, antifungal prophylaxis) variables have been identified as significant prognostic factors for IFI (Bow et al., 1995; Hammond et al., 2010; Michallet et al., 2011; Muhlemann et al., 2005; Rotstein et al., 1999).

The administration of systemic antifungal prophylaxis, routine use of chest and sinus computed tomography (CT), and the advent of safe and well-tolerated antifungal agents and non-culture-based diagnostic modalities (e.g., galactomannan enzyme immunoassay) have been introduced in clinical practice in the 2000s. Each of these modalities may have had an impact on the epidemiology of IFI among patients with hematologic malignancies. Contemporary data on the epidemiology, risk factors, and outcomes of IFI among nontransplant patients with acute leukemia are limited (Cordonnier et al., 2009; Cornely et al., 2007; Hahn-Ast et al., 2010; Hammond et al., 2010; Malagola et al., 2008; Vehreschild et al., 2007). We sought to review the epidemiology, risk factors, and outcomes of IFI in a contemporary 6-year cohort of adult patients with newly diagnosed acute myelogenous leukemia (AML) undergoing timed sequential induction chemotherapy, in a setting where primary antifungal prophylaxis was not used routinely and diagnostics were limited to culture- and histopathology-based, and imaging.

2. Materials and methods**2.1. Study design and patient population**

The study was approved by the Institutional Review Board of the Johns Hopkins Hospital (JHH). During the study period (1/1/2005–06/30/2010), 254 consecutive adult (>18 years) patients with newly diagnosed AML received 1 of 2 intensive, multi-agent induction regimens given in a timed sequential manner: i) AcDVP16 (cytarabine 667 mg/m² per day continuous infusion days 1–3, daunorubicin 45 mg/m² IV push days 1–3, and etoposide 400 mg/m² IV infusion over 6 h days 8–10) and ii) FLAM (flavopiridol 50 mg/m² over 1 h days 1–3, cytarabine 667 mg/m² per day IV continuous infusion days 1–3, and mitoxantrone 40 mg/m² IV infusion over 2 h day 9) (Karp et al., 2010; Karp et al., 2007). Patients presenting with poor risk features, including age ≥ 50 years, secondary AML (AML secondary to myelodysplastic syndrome [MDS], or myeloproliferative disorder, and treatment-related AML), and/or known adverse cytogenetics, were enrolled on a single-arm trial using FLAM

(Karp et al., 2007, 2010). All other patients were given the institutional standard (AcDVP16). Patients were identified through the JHH Sidney Kimmel Comprehensive Cancer Center Oncology Clinical Information System and pharmacy records. Patients with hematologic malignancies other than newly diagnosed AML, including but not limited to acute lymphocytic and promyelocytic leukemia, or those who received or were scheduled to receive an hematopoietic stem cell transplant within 6 months of their initial diagnosis, were excluded.

2.2. Prophylaxis regimens and treatment algorithms for neutropenic fever

Patients received acyclovir or valacyclovir for herpes prophylaxis and norfloxacin for gastrointestinal flora decontamination upon initiation of induction chemotherapy and until absolute neutrophil count (ANC) >100 cells/mm³. Streptococcal prophylaxis with ampicillin (or vancomycin in cases of penicillin allergy) was initiated on day 8 of induction chemotherapy until resolution of mucositis or broad spectrum antibacterial agent initiation for neutropenic fever. Primary antifungal prophylaxis was not routinely administered at our institution during the study period. With the first neutropenic fever, patients received piperacillin–tazobactam or cefepime (with the addition of vancomycin, based on the presence of severe mucositis, suspected central line infection, cellulitis, or risk for methicillin-resistant *Staphylococcus aureus* infection), as per institutional practices. For penicillin allergic patients, aztreonam and ciprofloxacin (or an aminoglycoside) were used alternatively. If patients remained febrile after 3–5 days on the above regimens, empirical antifungal therapy was initiated with liposomal amphotericin B, dosed at 5 mg/kg once daily. Surveillance throat and stool cultures were performed upon admission and weekly thereafter for all patients. For patients with neutropenic fever, blood and urine cultures and sinus and chest CT were obtained. Treatment was adjusted based on culture data for patients with positive culture results.

2.3. Data collection

The day of the first dose of induction chemotherapy was considered to be day 1. Data collected included demographics (age, gender, and ethnicity), year of AML diagnosis, evidence of extramedullary leukemia, chemotherapy regimen, prophylactic regimens, presence of mucositis (site, degree, and duration), and administration and duration of total parenteral nutrition. Baseline laboratory data included total white blood cell count (WBC), ANC, platelet count, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (± 3 days of day 1). Duration of ANC <500 and <100 cells/mm³ following chemotherapy was also recorded. Detailed data on surveillance throat and stool cultures for fungal organisms, including the site and duration of colonization, were collected. The first day of neutropenic fever occurrence and the empirical antibacterial and antifungal regimens administered were recorded. Bacterial, including bloodstream infections, pneumonia, and urinary tract infections, and viral infections and associated treatments were recorded. The majority of patients had 1 or more sinus or/and chest CT performed during their neutropenia period, and imaging reports were recorded as per radiology reading. Patients were followed for 6 weeks post induction chemotherapy initiation for development of an IFI. For those patients who were diagnosed with an IFI, the fungal pathogen (if available), site, timing of diagnosis post initiation of chemotherapy,

antifungal therapy administered (agent(s), dose and duration of therapy, and, in the event of multiple antifungal agents, either sequential or concomitant treatment) were collected. For patients with a possible sinus or/and pulmonary mould infection, imaging tests were retrospectively reviewed independently by 2 investigators (J.K. and D.N.).

2.4. Definitions

IFI were defined based on adjusted consensus guidelines (De Pauw et al., 2008; Nucci et al., 2010). For the diagnosis of possible IFI, the following CT findings were included: nodular lesions and/or consolidations/infiltrates. Fungal colonization was defined as the presence of organisms in surveillance throat and stool cultures without concomitant evidence of systemic infection from these organisms. Bacterial and viral infections were identified by the patient's treating physician on the basis of patients' symptoms, microbiologic data, and receipt of microbicide-specific treatment. Neutropenic fever was defined as a single temperature $\geq 38.3^{\circ}\text{C}$ or 2 episodes of $\geq 38.0^{\circ}\text{C}$ at least 2 h apart during neutropenia (ANC <500 cells/mm³) (Freifeld et al., 2011). Mucositis was defined according to clinical symptoms and signs of tissue inflammation involving the oropharynx or/and lower gastrointestinal tract, and graded according to the National Cancer Institute–Common Terminology Criteria (NCI-CTC) 3.0 and 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Extramedullary leukemia was defined as clinical, radiographic, or/and histopathologic evidence for leukemia involvement outside of the marrow compartment.

2.5. Statistical analysis

The primary objective of this study was to calculate the incidence proportion of IFI in adult patients with a new diagnosis of AML who received intensive, multi-agent induction timed sequential chemotherapy. Among the overall study population, rates of IFIs were calculated by dividing the number of patients who developed an IFI over the total number of patients treated for AML in the cohort year, and reported with exact 95% confidence intervals. Estimates were performed separately for patients with invasive candidiasis (IC) and invasive mould infections (IMI).

As a secondary endpoint, we sought to identify potential risk factors associated with the development of IFIs. IMI-free and IC-free survival were calculated as the time from the date of diagnosis to the date of IFI. Patients who did not develop an IFI were censored at their last known follow-up date. We examined IC-free and IMI-free survival separately due to the different pathophysiology and associated risks for IC and IMI. Overall survival was calculated as the time from the date of diagnosis to the date of death. Patients who were still alive were censored at their last known follow-up date. The database was locked on June 14, 2011. For each outcome, Cox proportional hazards models were run in a stepwise fashion such that variables from the univariate analyses with a P value ≤ 0.15 were included in a multivariate model. Analyses were completed using R version 2.14.2 (Vienna, Austria).

3. Results

A total of 254 patients with newly diagnosed AML who received induction chemotherapy with AcDVP16 or FLAM were identified (Table 1). Seventy-six (29.9%) patients were neutropenic upon presentation, 86 (34%) patients had secondary AML, and 180 (71%) and 74 (29%) patients were treated with AcDVP16 and FLAM, respectively. Twenty (7.9%) patients received antifungal prophylaxis with one of the following agents: fluconazole ($n = 9$), voriconazole ($n = 7$), and caspofungin ($n = 4$), upon the discretion of the treating physician, starting with initiation of chemotherapy until $\text{ANC} > 100 \text{ cells/mm}^3$.

A total of 123 (48.4%) IFI were identified: 14 (5.5%) patients were diagnosed with IC (13 with candidemia and 1 with biopsy-proven candidal uvular infection) and 108 (42.5%) patients with IMI; 1 patient (0.4%) had a bloodstream infection with *Rhodotorula* species. The proportions of patients with IFI identified during the study period by year are presented in Fig. 1A: there was a trend for more cases of IC diagnosed in 2009 and IMI diagnosed between 2007 and 2008, respectively. The cumulative probability of developing an IFI post induction chemotherapy initiation is demonstrated in Fig. 1B. The median time to diagnosis following chemotherapy initiation for IC and IMI was 17 (range: 5 to 26) and 12 days (range: -10 to 48), respectively ($P = 0.07$). After excluding 14 (12.9%) of 108 IMI (all possible, diagnosed prior to initiation of induction chemotherapy), the median time to IMI diagnosis was 14 days (range: 1 to 48).

Candida spp. other than *C. albicans* were almost exclusively identified in patients with candidemia, including *C. tropicalis* ($n = 4$), *C. guilliermondii* ($n = 3$), *C. glabrata* ($n = 2$), *C. kefyr* ($n = 2$), and *C. krusei* ($n = 1$). One patient had 2 different *Candida* spp. recovered from the same blood culture (*C. albicans* and *C. tropicalis*). Among 108 IMI identified, 4 (3.7%) were proven (*Mucor*, $n = 1$; *Lichtheimia*, $n = 1$; nonspeciated moulds, $n = 2$), 1 (0.9%) was probable (*Aspergillus fumigatus*), and 103 (95.4%) were considered possible lacking microbiologic confirmation (De Pauw et al., 2008; Nucci et al., 2010). Among patients with proven IMI, 2 involved the sinuses and 2 were disseminated. Among patients with a possible IMI, 98 involved the lungs and 5 the lungs and sinuses.

Among 246 patients with available information, 241 (98%) developed neutropenic fever at a median of 2 days (range: -17 to 24) of induction chemotherapy. Broad-spectrum antifungal agents were empirically administered in 221 (89.8%) patients, including liposomal amphotericin B (104/221, 47.1%), mould active azoles (83/221, 37.6%), and echinocandins (34/221, 15.4%). The median time to antifungal therapy initiation was 6 (range: -27 to 29), 0 (-19 to 17), and 6 days (-12 to 20) for liposomal amphotericin B, mould active azoles, and echinocandins, respectively. Excluding 11 patients with IMI, for whom the day of antifungal treatment initiation day was not known, 77 (of 97; 79.4%) were started on a systemical antifungal agent before or on the day of IMI diagnosis (median: 7 days; range: 0 to 39). Among 13 patients with candidemia, 10 (76.9%) had been started already on a broad-spectrum antifungal agent at a median of 18 days (range: 0 to 27) prior to diagnosis. The temporal associations of timing of IC and IMI diagnosis with the first neutropenic fever event, initiation of empirical antibacterial and antifungal treatment, mucositis, $\text{ANC} < 100 \text{ cells/mm}^3$, and neutrophil recovery are presented in Fig. 2. There was a trend for patients

with IC to be severely neutropenic earlier in their course ($P = 0.07$) and receive empirical treatment with a broad-spectrum antifungal agent ($P = 0.12$).

3.1. Risk factors for IFI

Risk factors for IC and IMI are shown in Table 2. One patient with *Rhodotorula* infection and 14 patients with IMI diagnosed prior to initiation of chemotherapy were excluded from the IC and IMI analyses, respectively. The following variables were included in the univariate analyses: age $\leq$ 50 years, gender, race (Caucasian versus other), AML from MDS versus other, FLAM versus AcDVP16, grade 3 mucositis, total parenteral nutrition, WBC $\leq$ 10,000 cells/mm³, ANC $\leq$ 100 cells/mm³, duration of ANC $<100/\text{mm}^3$ of $\leq$ 28 days, platelets $\leq$ 100,000 cells/mm³, creatinine $\leq$ 1.5 mg/dL, AST or/and ALT $\leq$ 120 U/mL, total bilirubin $\leq$ 2.0 mg/dL, and a composite variable for baseline organ dysfunction (defined as creatinine and AST or/and ALT $\leq$ 1.5 mg/dL and 120 U/mL, respectively), candidal colonization (number of *Candida* spp. and weeks $\leq$ 2, respectively), concomitant bacterial infections, bloodstream infections, and anti-fungal prophylaxis administration. There was a trend for patients with baseline organ dysfunction (hazard ratio [HR]: 2.9, $P = 0.07$) to develop IC, while lack of mucositis appeared to be protective (HR: 0.3, $P = 0.08$). In multivariate analyses for risk factors associated with IMI, female gender appeared to be protective for IMI (HR: 0.6, $P = 0.01$), while there was a trend for higher risk for IMI among Caucasian patients (HR: 1.7, $P = 0.10$).

3.2. Outcomes

To identify predictors of mortality, in addition to the above-described independent variables, we also examined the presence of IFI (IC versus IMI versus none) and primary antifungal treatment (liposomal amphotericin B versus other, voriconazole versus other) (Table 3). Older age (HR: 2.2, 95% confidence interval [CI] 1.5 to 3.4, $P < 0.001$), female gender (HR: 1.7, 95% CI 1.2 to 2.4, $P = 0.005$), and baseline organ dysfunction (HR: 2.4, 95% CI 1.5 to 3.8, $P < 0.001$) were the strongest mortality predictors in this series. Univariate analyses suggested that, compared to patients without an IFI, overall survival was worse for patients with IC (HR: 2.1, 95% CI 1.1 to 3.9, $P = 0.02$), followed by patients with a proven or probable IMI (HR: 1.9, 95% CI 0.6 to 6.0, $P = 0.29$). The overall 5-year survival for this cohort is presented in Fig. 3A. Patients with IC appeared to have the worst survival outcomes. Notably, patients without an IFI and those patients with a possible IMI appeared to have similar outcomes (HR: 1.0, 95% CI 0.7 to 1.4, $P = 0.95$). Survival analysis by 6 months suggested that death was predominately a late event among most patients with IC (Fig. 3B).

4. Discussion

This observational, retrospective study over a 6-year-period describes the epidemiology, risk factors, timing, and outcomes of IFI among adult patients treated with induction chemotherapy with AcDVP16 or FLAM for newly diagnosed AML. We report relatively low rates of IC despite lack of routine primary antifungal prophylaxis, albeit associated with poor long-term survival. High rates of IMI, the vast majority with a possible diagnosis, were

observed. Host-related variables (demographics and baseline organ dysfunction) were identified as the most significant risk factors for IFI and mortality predictors in this series.

Although the incidence of IC in this cohort was relatively low, despite lack of antifungal prophylaxis, patients with IC had significantly higher overall mortality compared to the rest of the study population. This may be due to the underlying compromised status of patients with IC, with the latter potentially representing a surrogate marker of disease severity. Patients with IC were more likely to be severely neutropenic and started on broad-spectrum antifungal agents earlier in their course. Notably, the majority of patients with IC received AcDVP16, which is associated with significant oral and lower gastrointestinal mucositis. Inability to regain mucosal integrity might have also contributed to poor outcomes. In fact, death appeared to be a later event among patients with IC. As prognosis heavily depends on the initial response to induction therapy, it is likely that patients with IC may be less likely to show complete remission and/or receive more aggressive consolidation chemotherapy, leading to worse long-term survival outcomes. Finally, although IC was identified as a significant mortality predictor in univariate analyses, its effect might have been diluted in multivariate analyses, perhaps due to the more significant impact of diverse host variables on the predicted outcomes. In fact, older age and baseline organ dysfunction were the most significant mortality predictors in this series, underlying the importance of the host in clinical outcomes.

Risk factor analysis for IC was limited due to the overall small number of patients. However, there was a trend for baseline organ dysfunction and chemotherapy-associated mucositis to be associated with higher risk for IC. The latter underscores the importance of mucosal integrity in patients with hematologic malignancies to prevent translocation of gut flora, including *Candida* spp., and disseminated infections. Male gender was the only significant risk factor for IMI among patients with AML. Hammond et al. (2010) first identified male gender as a possible risk factor for IFI in patients with hematologic malignancies. Whether this is associated with selection biases in terms of underlying disease severity and administered therapies or due to underlying biological or environmental reasons (e.g., higher iron loads or greater exposures to mould inhalation due to occupational hazards in male patients) remains to be defined. Although significant in univariate analyses and previous reports, the effect of neutropenia duration and organ dysfunction on the risk to develop an IMI was likely diluted in the multivariate analyses.

We observed a higher than previously reported incidence of IMI among patients with AML, mainly based on host, clinical, and radiographic findings. This may be due, in part, to the high-risk features of AML patients cared for in our institution (Karp et al., 2007, 2010). In addition, chest and sinus CTs are frequently and promptly obtained on our patients with neutropenic fever, which might have contributed to the early detection of possible IMI. Although detailed review of these patients' medical records was performed to confirm the diagnosis of a possible IMI by 2 independent investigators, it is likely that some fraction of these patients did not have an IMI. In fact, survival analyses demonstrated that outcomes were similar between patients with a possible IMI and those patients without a diagnosis of an IFI. It is also possible that a number of these patients did have an IMI and that timely initiation of appropriate preemptive antifungal treatment led to improved clinical outcomes.

Microbiologic confirmation was limited in this cohort, as patients with leukemia are rarely able to produce sputum (Boersma et al., 2007; Horvath and Dummer, 1996; Peikert et al., 2005; Yu et al., 1986), diagnostic bronchoscopies were scarcely performed, and the use of nonculture antigen-based diagnostics (e.g., galactomannan enzyme immunoassay) was very limited during the study period.

Indeed, lack of microbiologic confirmation in a large number of IMI was one of the major limitations of this study. In addition, our findings may not be directly applicable to other centers, as we are a tertiary-care center with a particularly high-risk AML population that received 2 specific intensive, multi-agent induction regimens given in a timed sequential manner. Finally, this study reports results from an era when antifungal prophylaxis and non-culture-based diagnostic tests were not routinely used.

We report a low incidence of IC associated with high 5-year mortality rates, in a contemporary cohort of AML patients treated with intensive antileukemic therapy in our center. Lack of microbiologic confirmation in the vast majority of IMI limits our ability to make meaningful conclusions. Strategic use of systemic antifungal prophylaxis and nonculture antigen-based diagnostics may lead to lower rates of IFI, prompt initiation of targeted treatment, and possibly improved survival outcomes.

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Fig. 1.

(A) Rates of invasive fungal infections (invasive candidiasis [IC] and invasive mould infections [IMI]) by year during the study period. Segments represent exact 95% confidence intervals. (B) Cumulative probability for IC and IMI during the study period.

Fig. 2. Temporal association of the first neutropenic fever event and relevant clinical and laboratory variables. Data for neutropenic fever were available for 246 patients (241 of 246 had evidence of neutropenic fever). *P*-values are for Kruskal-Wallis tests for differences in distributions between groups.

Fig. 3.

Kaplan–Meier survival curves: results are presented for patients without an invasive fungal infection (IFI) and separately for patients with invasive candidiasis (IC), proven/probable invasive mould infection (IMI), and possible IMI. (A) Five years post induction chemotherapy. (B) Six months post induction chemotherapy.

Table 1

Patient characteristics.

	No IFI, <i>n</i> = 131 (%)	Invasive candidiasis ^a , <i>n</i> = 15 (%)	Invasive mould infection, <i>n</i> = 108 (%)
<i>Demographics</i>			
Age (years), median (range)	54 (20–72)	54 (33–70)	54 (20–78)
Gender, female	66 (50)	9 (60)	35 (32)
Race, Caucasian	102 (78)	11 (73)	95 (88)
<i>AML-related variables</i>			
AML from MDS	46 (35)	6 (40)	34 (31)
Extramedullary leukemia	8 (6)	0 (0)	9 (8)
Blasts, % on day 1	17.5 (1–96)	37.5 (2–100)	23 (1–96)
<i>Treatment-related variables</i>			
Chemotherapy regimen, AcDVP16 ^b	89 (68)	11 (73)	80 (74)
Mucositis, all grades	77 (59)	13 (87)	60 (56)
Mucositis, grade 3	32 (42)	9 (69)	34 (57)
Mucositis, lower gastrointestinal tract	51 (67)	12 (92)	33 (55)
Total parenteral nutrition	28 (22)	5 (33)	25 (23)
<i>Laboratory variables^c, median (range)</i>			
WBC, >10,000 cells/mm ³	25 (19)	2 (13)	19 (18)
ANC, cells/mm ³	601 (0–26,575)	411 (0–4577)	691 (0–23,134)
Days of ANC <100 cells/mm ³	25 (7–69)	24.5 (17–55)	23 (9–55)
Platelet count, ×1000 cells/mm ³	59 (7–567)	41 (16–298)	45 (5–435)
Creatinine, mg/dL	0.8 (0.5–2.5)	0.8 (0.3–1.6)	0.8 (0.3–6.9)
AST, U/mL	23.5 (7–163)	26 (13–125)	21.5 (5–222)
ALT, U/mL	36 (7–516)	66 (17–277)	24 (5–222)
Total bilirubin, mg/dL	0.7 (0.1–3.5)	0.9 (0.3–2.2)	0.7 (0.1–6.8)
<i>Colonization</i>			
<i>Candida</i> species	112 (85)	14 (93)	101 (94)
Number of <i>Candida</i> species, 2	51 (46)	7 (50)	60 (60)
Weeks of <i>Candida</i> colonization, 2	33 (30)	8 (57)	33 (33)

Values are median (range).

Values are shown as *n* (%) unless otherwise indicated.

AML = Acute myelogenous leukemia; ANC = absolute neutrophil count; MDS = myelodysplastic syndrome; AcDVP16 = cytarabine, daunorubicin, and etoposide; WBC = white blood cell count; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

^aOne patient with bloodstream infection with *Rhodotorula* spp. was included.

^bThe remaining patients were treated with FLAM (flavopiridol, cytarabine, and mitoxantrone).

^cBaseline laboratory variables were collected within 3 days of day 1 (day of induction treatment initiation).

Table 2

Risk factors for invasive candidiasis and mould infections among patients with new diagnosis of acute myelogenous leukemia post induction chemotherapy.*

Variables	Invasive candidiasis			Invasive mould infections		
	Univariate analysis		P value	Univariate analysis		P value
	HR	95% CI		HR	95% CI	
Gender, female				0.6	0.4–0.9	0.01
Race, Caucasian versus other				1.7	0.9–3.1	0.08
Chemotherapy regimen, FLAM versus AcDVP16				0.7	0.4–1.1	0.13
Mucositis grade 3, no versus yes	0.3	0.1–1.2	0.08	0.3	0.06–1.2	0.08
Colonization with <i>Candida</i> spp., Yes versus No				2.1	0.9–4.9	0.09
Colonization with <i>Candida</i> spp. 2 sites, yes versus no				1.9	0.8–4.4	0.14
ANC, < versus 100 cells/mm ³				1.6	0.8–2.9	0.12
Creatinine, versus <1.5 mg/dL				2.0	0.9–4.7	0.09
Baseline organ dysfunction, yes versus no	2.9	0.9–9.1	0.08	2.9	0.9–9.4	0.07
Concomitant bacterial infections, no versus yes				0.7	0.5–1.1	0.13

HR = Hazard ratio; 95% CI = confidence interval; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; FLAM = flavopiridol, cytarabine, and mitoxantrone; AcDVP16 = cytarabine, daunorubicin, and etoposide; WBC = white blood cell count; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

[†] Baseline laboratory variables were collected within 3 days of day 1 (day of induction treatment initiation).

* Only results with $P < 0.15$ are presented.

Table 3

Mortality predictors among patients with acute myelogenous leukemia post induction chemotherapy.*

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, years, versus <50 years	2.2	1.5–3.3	<0.0001	2.2	1.5–3.4	<0.001
Gender, female	1.4	1.0–2.0	0.03	1.7	1.2–2.4	0.005
AML from MDS, no versus yes	0.7	0.5–0.9	0.03			
Chemotherapy regimen, FLAM versus AcDVP16	1.4	0.9, 2.1	0.06			
IC versus other	2.1	1.1–3.8	0.02	1.6	0.9–3.0	0.13
Creatinine, versus <1.5 mg/dL	2.5	1.2–5.2	0.01			
AST or/and ALT, versus <120 U/mL	2.0	1.0–3.9	0.05			
Total bilirubin, versus <2.0 mg/dL	2.3	1.2, 4.1	0.007			
Baseline organ dysfunction, yes versus no	2.2	1.4–3.4	<0.001	2.4	1.5–3.8	<0.001

HR=Hazard ratio; 95% CI=confidence interval; AML=acute myelogenous leukemia; ANC = absolute neutrophil count; MDS = myelodysplastic syndrome; FLAM = flavopiridol, cytarabine, and mitoxantrone; AcDVP16 = cytarabine, daunorubicin, and etoposide; IMI = invasive mould infection; IC = invasive candidiasis; WBC = white blood cell count; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

[†] Baseline laboratory variables were collected within 3 days of day 1 (day of induction treatment initiation).

* Only results with $P < 0.15$ are presented.