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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.

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

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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/m^2 per day continuous infusion days 1–3, daunorubicin 45 mg/m^2 IV push days 1–3, and etoposide 400 mg/m^2 IV infusion over 6 h days 8–10) and ii) FLAM (flavopiridol 50 mg/m^2 over 1 h days 1–3, cytarabine 667 mg/m^2 per day IV continuous infusion days 1–3, and mitoxantrone 40 mg/m^2 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/mm^3. 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/mm^3 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 ≥38.3 °C or 2 episodes of ≥38.0 °C at least 2 h apart during neutropenia (ANC <500 cells/mm^3) (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