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Original Article

Evaluation of the implementation rate of primary antifungal prophylaxis and the prognosis of invasive fungal disease in acute leukemia patients in China

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ABSTRACT

Background: Invasive fungal disease (IFD) is a major complication of acute leukemia, thus primary antifungal prophylaxis (PAP) is recommended by guidelines. Nevertheless, guidelines might not be commonly followed in developing countries due to economic factors. The primary objectives were to evaluate the implementation rate of PAP in acute leukemia patients in China and to compare the prognosis of IFD with and without PAP. The secondary objectives were to investigate the safety of PAP, clinical characteristics of IFDs and risk factors of breakthrough.

Methods: This was a retrospective observational single-center study, including non-M3 acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) patients receiving uniform induction or salvage chemotherapy between 2012 and 2016.

Results: There were 29.4% of patients without PAP among a total of 248 cases. The incidence of breakthrough proven/probable/possible IFDs was 24.7%, 6.5%, 5.5%, 5.4% and 5.3% in control (no prophylaxis), fluconazole, itraconazole, voriconazole and posaconazole group respectively ($P = 0.007$), while the percentage of patients requiring empirical or pre-emptive therapy was 54.8%, 45.7%, 23.3%, 18.9%, 10.5% respectively ($P < 0.001$). PAP could also significantly improve IFD-free survival ($P < 0.001$) and reduce 90-day overall mortality in patients on AML salvage regimen ($P = 0.021$). There were no statistical differences in PAP-related adverse events. Past history of IFD (OR 9.5, $P = 0.006$) was confirmed to be independent risk factors.

Conclusions: There are a considerable number of acute leukemia patients without PAP in China, who have higher IFD incidence, increased empiric/pre-emptive antifungal drug use and worse IFD-free survival.

1. Introduction

Invasive fungal disease (IFD) is a major complication of prolonged neutropenia during chemotherapy for acute leukemia. Despite the rapid development of new-generation antifungal agents, IFD-associated morbidity and mortality remains to be remarkable [1–4]. Patients with IFDs often undergo interrupted, delayed or changed chemotherapy regimen, which may undermine long-term survival [5]. In particular, remission induction chemotherapy has been suggested to be the highest-risk phase for development of IFDs in patients undergoing initial treatment [1,6,7]. The incidence of IFDs during salvage chemotherapy among

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refractory or relapsed patients was reported to be even greater, given the high intensity of salvage regimen [8,9].

In view of challenges in early diagnosis of IFDs and the poor outcomes of delayed treatment, prophylaxis in patients under high risk, including acute leukemia patients undergoing induction and salvage chemotherapy, has been proposed and investigated. Primary antifungal prophylaxis (PAP) during neutropenia has shown satisfactory efficacy and tolerability, and thus has been strongly recommended by international guidelines. However, to the best of our knowledge, there has been no similar guideline in China up to now. Although attempts have been made to apply the "ready-made" experiences from Western countries, PAP practice is far more complicated in developing countries where medical resources might not satisfy the need of each patient [10–12]. Considering the high cost of antifungal agents, clinical benefits have to be weighed against financial burden under most circumstances. Non-selective broad-spectrum primary prophylaxis has also raised considerable concerns over the toxicity, drug interaction and possibly emerging fungal resistance [13,14]. Consequently, PAP might not be implemented as common as expected. In fact, its current status remains unknown in countries with relatively low per capita health care spending. Furthermore, few of the published real-world data [15–18] assessing PAP could exclude potential confounding factor disturbance from diversity in primary disease treatment, while only limited studies [19–23] have been specifically focused on certain chemotherapy regimens. Additionally, despite substantial research regarding acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) [15–17], much less has been known about PAP in adults with acute lymphocytic leukemia (ALL) [24–26].

The primary objectives of this retrospective observational single-center study were to evaluate the implementation rate of PAP by azoles with particular attention to acute leukemia patients receiving uniform induction or salvage chemotherapy in China and to compare the prognosis of IFD with and without PAP. The secondary objectives were to investigate the safety of PAP, clinical characteristics of IFDs and risk factors of breakthrough.

2. Patient and methods

2.1. Patients and study design

We included all consecutive non-M3 AML and ALL patients aged over 14 who underwent certain induction or salvage chemotherapy regimens (Table 1) between January 2012 and June 2016 in the department of hematology, Peking Union Medical College Hospital, Beijing, China, which is a 2300-bed, university-affiliated, tertiary hospital. For patients admitted for induction or salvage chemotherapy more than once, only the first cycle was included. We included such 3 regimens for the following reasons. First, DA and VDLD/VDCDL were our conventional chemotherapy for initially treated non-M3 AML and ALL, respectively. CLAG was our most commonly used therapy for refractory or relapsed AML during the recent 5 years. Patients undergoing these 3 regimens accounted for more than 90% of all acute leukemia cases in our hospital. Second, they are among the first-line chemotherapy regimens recommended by National Comprehensive Cancer Network (NCCN) Guidelines [27,28]. Third, as highly aggressive regimens, they are often associated with prolonged neutropenia and further resulted in high risk of IFD [9,29,30]. The exclusion criteria were systemic antifungal treatment within 30 days prior to chemotherapy and concomitant or subsequent use of more than one agents for PAP. All the treatments were performed in conventional wards without laminar flow and there were no changes in hygiene conditions during the observed period. The protocol was approved by the Ethics Committee.

Table 1
Chemotherapy regimen.

Diagnosis	Chemotherapy regimen	
AML	Induction: DA	DNR 60 mg/(m^2·d), d1-3 AraC 100 mg/m^2, q12h, d1-7
	Salvage: CLAG	Cladribine 5 mg/(m^2·d), d1-5 AraC 2 mg/(m^2·d), q12h, d1-5 GCSF 300 μg/d, d0-5
ALL	<40 yo: VDLD	VDS 4 mg, d1,8,15,22 DEX 10 mg/m^2, d1-14 L-asparaginase 3750U, d1, 15 DNR 40 mg/m^2, d1-3 TKI (if *Ph*+)
	>40 yo: VDCDL	VDS 4 mg d1, 8, 15, 22 DEX 10 mg/m^2, d1-7, d11-17 CTX 1000–1200 mg/m^2, d11,15 L-asparaginase 3750U, d5, 19 DNR 40 mg/m^2, d1-3, d15-16 TKI (if *Ph*+)

Abbreviations: DNR, daunorubicin; AraC, cytarabine; GCSF, granulocyte colony stimulating factor; yo, years old; VDS, vindesine; DEX, dexamethasone; CTX, cyclophosphamide; TKI, tyrosine kinase inhibitor; *Ph*, *Philadelphia* chromosome.

PAP strategies were consisted of fluconazole 200 mg daily, itraconazole 2.5 mg/kg twice daily, voriconazole 200 mg twice daily and posaconazole 200 mg 3 times daily. All of the antifungal agents were given per oral if possible. Prophylaxis was started at the occurrence of neutropenia (defined as neutrophil counts $< 0.5 \times 10^9$/L) and continued until resolution of neutropenia (defined as neutrophil counts $\geq 0.5 \times 10^9$/L for at least 2 consecutive days). Sometimes PAP extended beyond neutropenic phase depending on physicians' judgments. For patients with baseline neutropenia (defined as the presence of neutropenia before chemotherapy), prophylaxis was applied since the beginning of chemotherapy. PAP was also discontinued if there were confirmed or suspected IFDs or intolerable drug-related adverse events.

2.2. Diagnostic work-up of IFDs and antifungal treatment

In the event of persistent febrile (axillary temperature >38.5 °C) neutropenia unresponsive to broad-spectrum antibiotics for >72 h or with recurrent fever, the diagnostic work-up included blood culture, 1,3-β-D-glucan (G) test and galactomannan (GM) test in serum, and a thoracic computed tomography (CT). Blood culture was repeated at least 3 times. A serum test was considered as positive with a cut-off value ≥ 60 ng/ml for G test (Fungitell, USA) and an index ≥0.5 for GM test in two consecutive blood samples and was not evaluated in patients on piperacillin/tazobactam to avoid false positive. Sputum microscopy and culture, cerebrospinal fluid (CSF) test and cranial MRI, nasal swab and paranasal sinus CT, abdominal ultrasound and CT would also be performed as indicated. Invasive fungal disease was diagnosed according to the definition of the consensus group of the European Organization for Research and Treatment of Cancer Invasive Fungal Infections Cooperative Group (EORTC) [10].

Targeted antifungal therapy would be started as soon as a proven/probable/possible IFD was diagnosed. We would perform pre-emptive antifungal therapy on condition that any clinical and/or microbiological findings were suspected to be associated with IFD but failed to meet the diagnostic criteria. In the case of a negative diagnostic work-up and persistent febrile neutropenia for >120 h, the work-up was repeated and empirical antifungal therapy was indicated [10]. Invasive procedures, such as bronchoscope, would be carried out, if the repeated diagnostic work-up remained negative twice but clinical conditions deteriorated despite empirical therapy. Targeted/empirical/pre-emptive antifungal therapy consisted of intravenous administration of amphotericin B 0.7 mg/