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Short communication

# Chronic disseminated candidiasis and acute leukemia: Impact on survival and hematopoietic stem cell transplantation agenda

## *Candidose disséminée chronique et leucémie aiguë : impact sur la survie et l'agenda de transplantation de cellules souches hématopoïétiques*

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**Abstract**

*Objectives.* – To study the management of chronic disseminated candidiasis (CDC) in patients presenting with acute leukemia.

*Patients and methods.* – Single-center retrospective study of acute leukemia patients (2006–2015) to investigate three aspects of CDC: its impact on the time interval between diagnosis and hematopoietic stem cell transplantation, when required (non-parametric Wilcoxon-Mann-Whitney test); its impact on overall survival (Cox proportional hazard regression model); antifungal therapeutic strategies implemented.

*Results.* – A total of 639 patients presenting with acute leukemia were included; 144 were transplanted and 29 developed CDC. CDC did not significantly increase the time interval between diagnosis and transplantation, nor did it impact the overall survival of recipients. An improved overall survival was observed in non-transplanted acute leukemia patients presenting with CDC.

*Conclusion.* – CDC should not postpone transplantation if antifungal treatment is optimized.


*Keywords:* Chronic disseminated candidiasis; *Candida*; Allogeneic transplantation

**Résumé**

*Objectifs.* – Étudier la candidose disséminée chronique (CDC) associée à une leucémie aiguë.

*Patients et méthodes.* – Étude monocentrique rétrospective (2006–2015) chez des patients atteints de leucémie aiguë évaluant trois aspects de la CDC : son impact sur l'intervalle diagnostic-transplantation de cellules souches hématopoïétiques, quand requise (test non paramétrique de Wilcoxon-Mann-Whitney); son impact sur le pronostic global des patients (modèle de régression de Cox) ; stratégies antifongiques utilisées.

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*Résultats.* – Au total, 639 patients atteints de leucémies aiguës ont été inclus ; 144 ont reçu une transplantation et 29 ont présenté une CDC. La CDC n'a pas significativement augmenté l'intervalle diagnostic-transplantation et n'a pas impacté la survie globale des patients transplantés. Une meilleure survie globale a été observée chez les patients atteints de leucémie aiguë non transplantés présentant une CDC.

*Conclusion.* – La CDC ne doit pas différer l'agenda de transplantation si le traitement antifongique est optimisé.


*Mots clés :* Candidose disséminée chronique ; *Candida* ; Transplantation allogénique

## 1. Introduction

Chronic disseminated candidiasis (CDC), also known as hepatosplenic candidiasis, is a biphasic entity with a primary invasive candidiasis phase with *Candida* spp. metastases after translocation from the digestive tract to the portal circulation. The second phase is the inflammatory syndrome due to neutrophil recovery, sufficient to clear *Candida* spp. metastases. The incidence of CDC in patients presenting with acute leukemia ranges from 4.5% to 6.8%, and from 3% to 9% in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1,2]. Over the past decade, significant advances have been made in the understanding of CDC in the hematological setting. CDC refractory symptoms observed in patients receiving appropriate antifungal therapy are part of an immune reconstitution inflammatory syndrome (IRIS) defined as an enhanced immune pathogen-specific response resulting in the development of aseptic granuloma. IRIS diagnosis is based on the occurrence or worsening of clinical or radiological manifestations in the absence of newly positive mycological cultures or biomarkers [3]. Adjuvant corticosteroid treatment, in addition to antifungal therapy, was shown to be effective on CDC-related symptoms and inflammatory response [4]. Another recent report demonstrated the efficacy of thalidomide, an immunomodulatory drug, in controlling IRIS-related CDC [5].

Prior studies also reported that the underlying condition prevailed over CDC. Indeed, CDC did not limit the use of further intensive chemotherapy to achieve sustained remission or did not contraindicate allogeneic HSCT [1,4,6–9]. However, most studies did not address the issue of the time interval between CDC onset and allogeneic HSCT. Safely carrying out allogeneic HSCT after obtaining full remission impacts the overall outcome: for patients with otherwise equal risks, the percentage of disease-free survival decreases with a longer time from diagnosis to transplantation [10].

We addressed the issue of the optimal time interval between acute leukemia diagnosis and allogeneic HSCT in patients presenting with CDC, and the impact of CDC on long-term survival of non-transplanted acute leukemia patients.

## 2. Patients and methods

We conducted a single-center retrospective study from 2006 to 2015 to record all symptomatic CDC among 639 adult patients presenting with acute leukemia, including 144 patients who underwent allogeneic HSCT. Diagnosis of CDC was established as per the revised definitions of invasive fungal disease issued by the EORTC/MSG and ESCMID group [11]. As CDC is an uncommon complication, statistical methods allowing comparison of small population samples were used (< 30 individuals). To compare the time interval between acute leukemia diagnosis and allogeneic HSCT according to CDC occurrence, a non-parametric Wilcoxon-Mann-Whitney test was applied using random permutations without repetition of generated allotransplanted patient subgroups without CDC (2000), proportionally sized to the pre-transplant-CDC group ($n = 15/144$ patients). To compare the long-term survival rate of the acute leukemia population according to CDC occurrence, a Cox proportional hazard regression model was applied using random permutations without repetition of generated acute myeloid leukemia patient subgroups (10,000 for the whole acute leukemia population, 5000 for the non-allotransplanted subset, and 2000 for the allotransplanted subset), proportionally sized to the corresponding CDC subgroups ($n = 29/639$, $n = 2/495$, and $n = 17/144$ patients for the whole acute leukemia population, for the non-allotransplanted, and allotransplanted subsets, respectively). Hazard ratio (HR) and *P*-value were expressed as median HR (mHR) and median *P*-value (mP) respectively, calculated from each permutation group. Both mHR and mP were expressed within the interquartile range (IQR) of first (Q1) and third (Q3) quartiles [Q1–Q3] (R software version 3.0.2). The study was approved by the local ethics committee (Comité d'Éthique, Hospices Civils de Lyon). Considering the retrospective observational nature of the study and the lack of modification in the general management of these patients, the need for informed consent was waived.

## 3. Results

Demographics and hematological characteristics of CDC patients are summarized in Table 1. Twenty-nine (4.5%) cases of CDC were included among 639 adult patients presenting with acute leukemia managed at our center; 144 patients subsequently underwent allogeneic HSCT (Fig. 1). The diagnosis was confirmed in seven cases (24%) and probable in 22 cases (76%) (Table 1). CDC developed on antifungal prophylaxis in 10 patients (34.5%), among whom eight (27.6%) were receiving posaconazole prophylaxis (liquid formulation). Patients received an average of three (range 1–5) different antifungal drugs due to persistent fever. The median treatment duration

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