RETROSPECTIVE EVALUATION of CHRONIC DISSEMINATED CANDIDIASIS in PATIENTS with HEMATOLOGIC MALIGNANCIES: EPIDEMIOLOGY, CLINICAL AND TREATMENT

SCIENTIFIC BOARD:

Livio Pagano (Italy), Mario Tumbarello (Italy), Emmanuel Roilides (Greece), Habip Gedik (Turkey), Marco Picardi (Italy), Christophe Hennequin (France), Maurizio Sanguinetti (Italy)

Introduction

The percentage of patients suffering from hematological malignancies that develop deep fungal infections has increased dramatically in recent decades. *Candida* spp. for many decades it has been the most frequent cause of invasive fungal infection particularly in neutropenic patients, although in recent years its incidence rate has been significantly reduced. The main clinical manifestation of infection due to *Candida* is blood stream infection, while the observation of late manifestations as chronic disseminated candidiasis (CDC) is extremely rare. The mortality rate related to this last kind of infectious is very low, on the contrary, the main problem of this complication is related to the delay in following treatment of malignancy with a high risk of malignancy progression.

Until a few years ago, the treatment of choice was the deoxycolate Amphotericin-B followed by oral fluconazole for a prolonged period (at least 4-6 months). However, the long treatment period leads to increased complications due to drug toxicity. In recent years with the introduction of a new generation of antifungal drugs (lipid formulation of AmB, azoles of new generation and echinocandins) the clinical history of this complication has changed considerably with the possibility of more precocious resolutions.

However, the rarity of observation of complication is unable to make prospective randomized clinical trial that can give clear answers, and also the recent ESCMID guidelines for CDC do not give indications that may be unique.

This study aims to assess whether the incidence of this complication has really declined in recent years, if the new diagnostic techniques have allowed an improvement of the diagnosis, and whether the introduction of new antifungal agents has improved the management of patients with a reduction in the duration of treatment with the elimination of further delays in the programs of chemotherapy regimen.

The aims and objectives of the project

- The purpose of this study is to record all cases of chronic disseminated candidiasis (CDC) certain and probable observed in patients with malignancy (particularly neutropenic) observed over the past 10 years. Both pediatric and adult patients with hematological malignancies can be enrolled. In order to collect data about:
  - Epidemiology and Incidence
  - Clinical and laboratory features
  - Treatments
  - Outcome
  - Impact on the treatment of underlying hematological malignancy

Study Design

- Retrospective, multicenter, non-interventional registry.
- Inclusion criteria: all patients with hematologic malignancies at any stage of the disease (including those undergoing HSCT transplant procedures) observed in each center and care during the last 10 years. We will identify all diagnoses of CDC at each center from 1 January 2006 until December 2016; the clinical, microbiological, diagnostic and therapeutic procedures operate on these patients will then be collected in an anonymous data collection sheet.
- An electronic CRF will be made. (see attached sheet).

- Data collection for each event will be made according to the regulations of each Country of the participating center. after written informed consent if the patient is still alive.
- The data obtained will be recorded with a proper observance of privacy laws.
- This study received the approval of the Ethic Committee of Catholic University of Sacred Hearth, Roma , Italy.

Materials and Methods

This is a retrospective clinical-epidemiological study, with the objective of evaluating the problem of CDC in adult and pediatric patients with malignancies. The literature on this topic is extremely low, despite the infections remain a major cause of mortality and morbidity in these patients, and it is especially dated, since the studies carried out mostly in the early 2000s, when the regimens were less aggressive and diagnostic methods less effective.

Diagnosis of CDC results really difficult and not all the current literature agree with a correct definition of the criteria for a stratification of the different levels of certainly. We propone the following criteria for definition of proven/probable/possible CDC:

- In any case : hematological malignancy + one episode of neutropenia (deep <500 and prolonged > 10 days) in the previous 2 months

Plus

- Hepatic/splenic lesions microbiologically/pathologically documented = >Definite
- Hepatic/splenic lesions + previous candidemia => Probable
- Hepatic/splenic lesions alone => Possible (we can discuss if include or not this entity)

Given the rarity of fungal complication, the study in question makes provision for the enrollment of 100 - 200 cases.

In all patients is planned to compile a detailed epidemiological card, which will be reported the phase of the disease, the type of chemotherapy, the execution of an autologous or allogeneic HSCT and its conditioning, the response to chemotherapy for underlying HM, the possible risk factors for the onset of infection (steroid therapy, CVC placement and/or urinary catheter, prolonged neutropenia, mucositis, presence of other diseases

such as diabetes, kidney failure, liver failure, lung diseases, infectious prophylaxis established (antibiotics and antifungals), the results of surveillance cultures for fungi such as nasal, oropharyngeal, urinalysis and stool), the characteristics of clinic-laboratory, microbiological and instrumental infection detected by tests performed routinely (exams microbiologists, chemical, radiological, antigenic), the use of G-CSF, the data regarding the antifungal treatment and the course of infection.

Patients were observed for at least 6 months in order to evaluate the outcome of CDC and the efficacy of treatment. Mortality due to CDC was considered when patients died within 12 weeks after the onset of fever and had microbiological, histological or clinical evidence of an active IFI if other potential causes of death could be excluded by the physician responsible.

Once obtained all cases, it will be analyzed statistically or if the number of cases obtained will be small only observational report will be made. In case the number of recorded cases will be higher we can proceed to identify risk factors in an analysis.

Publication policy

The results will be the subject of one or more publications on major international scientific journals that deal with topics related to hematology, infectious diseases and microbiology. Furthermore, the results will be submitted for presentation at a major national and international conferences in hematology/infectious diseases/microbiology .

Each center will be entitled to an author's name on the "main article". For centers that help with more case studies, if possible, will include a second co-author.

The data are owned by all the researchers involved in the study and who may seek to use them upon request to the coordinating center, once completed the study and validated from the point of view of a scientific board.

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Prof Livio Pagano