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Defining clinical failure for salvage studies

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In patients with invasive aspergillosis (IA), there are numerous clinical settings where stable disease or progression of findings or deterioration of the patient's condition does not indicate failure, and subsequent response to a 'salvage' antifungal is not necessarily attributable to this drug. Many patients, in whom pulmonary aspergillosis emerges during profound neutropenia, show enlargement of their lesions on computer tomography (CT) scans, eventually accompanied by clinical deterioration, during hematopoietic recovery. This may in fact represent the recruitment of neutrophils and monocytes to the pulmonary 'battlefield', resulting in a favorable clinical outcome also without changing antifungal treatment. Infarcted tissue may contain vital filamentous fungi, because it is poorly penetrated by the antifungal, not indicating a lack of efficacy of this drug against the respective fungal pathogen. In patients treated with an echinocandin, serum galactomannan levels may increase despite successful treatment. Piperacillin-tazobactam or other semi-synthetic beta-lactam antibiotics may cause false positive serum *Aspergillus* galactomannan levels. Patients primarily treated with a lipid formulation of AmB (LF-AmB), who are switched to a 'salvage' antifungal, will unequivocally receive a combination therapy due to the persistence of high LF-AmB concentrations in tissue. Criteria to define 'clinical refractoriness', 'resistance', 'non-response' or 'failure' respectively should be re-defined. One option to establish a more valid definition would be to use a composite score including clinical as well as radiological and microbiological or mycological criteria. The latter may include non-culture based methods such as serum galactomannan. Assessment should not be made earlier than after seven days of full-dose systemic antifungal treatment. However, in individual cases, e.g. a patient with hematopoietic recovery, who shows an increasing volume of pulmonary aspergillosis and clinical deterioration, it may be recommended to refrain from switching the patient to another regimen and continue the current antifungal treatment for another seven days before failure is stated. Clinical studies on second-line antifungal treatment for IA should be randomized and blinded, patients should be evaluated separately with respect to their reason for 'failure' of primary antifungal treatment, and stratified according to their previous antifungal treatment. Ideally, the first-line regimen would be standardized. Host criteria such as neutropenia or graft-versus-host disease (GVHD) should be clearly defined and documented with respect to their course over time, and patients should be stratified according to these criteria. A three-arm study (continuation of primary

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antifungal vs. combination of primary antifungal with a 'salvage' drug vs. the 'salvage' drug alone) would be ideal.

Keywords Invasive aspergillosis, definition, failure, trial design

Introduction

During the past decade, a number of new broad-spectrum antifungal agents have been developed and approved for clinical use. Voriconazole has been approved for primary therapy of invasive aspergillosis (IA), after a properly designed, prospective randomized clinical trial had shown significantly superior rates of complete and partial response as well as a survival benefit in comparison to amphotericin B deoxycholate [1]. Several other antifungals such as caspofungin, posaconazole, liposomal amphotericin B, amphotericin B lipid complex or amphotericin B colloidal dispersion have been licensed for treatment of patients with invasive fungal infections who are refractory to (or intolerant of) other antifungal agents. Their efficacy in patients with refractory aspergillosis has been studied in 'salvage' trials which have, however, shown inconsistent results or response rates that later turned out to be irreproducible in normal clinical practice [2]. For a few of these antifungals, prospective randomized studies have been conducted to evaluate their activity for primary treatment of IA [3–6], whereas for others this activity can only indirectly be assessed by separately analyzing response rates in patients intolerant of other antifungals from 'salvage' trials. In these patients it can be assumed that the second-line antifungal more or less represents the primary treatment. Another patient group allowing a speculation on the efficacy of these drugs for first-line treatment is the subgroup of patients entered into one of the major clinical studies on empirical antifungal therapy in whom shortly after inclusion a invasive fungal infection has been documented [7]. Overall, the efficacy of the majority of antifungals for the treatment of IA is not precisely defined.

Testing newly developed antifungals for their clinical efficacy in patients with IA requires second-line or 'salvage' studies, since testing such a drug for first-line treatment in a randomized fashion against an antifungal licensed for primary treatment would be unethical. However, there are substantial pitfalls in the design of these trials. These pitfalls may have a tremendous impact on the assessment of the efficacy of the drug.

Problems defining 'resistance' or 'refractoriness' in patients with invasive aspergillosis

In patients with proven IA, there may be a clearly documented resistance to a particular antifungal agent. Examples for this would be a mycologically proven infection caused by *Aspergillus terreus* in a patient treated with amphotericin B [8], cerebral aspergillosis in a patient treated with an antifungal which is not capable of achieving sufficient concentrations in brain tissue, or progressive aspergillosis in another specific organ where insufficient concentrations of the antifungal are achieved [9], or aspergillosis due to an isolate which is shown to be resistant to itraconazole [10].

Undoubtedly, clinical failure of primary antifungal treatment may be present already after a few days of therapy in patients with IA. In the randomized clinical comparison of voriconazole and amphotericin B deoxycholate, patients whose infection progressed under amphotericin B treatment could be switched to another antifungal. In these patients, it has been shown that the switch to another licensed antifungal has not been able to equalize to overall clinical outcome [11]. However, it is extremely difficult to identify these 'true non-responders' early during antifungal treatment.

Clinical settings of 'pseudo-failure'

In contrast, there are numerous clinical settings where progression of findings or deterioration of the patient's condition does not necessarily reflect failure, and, conversely, response to a 'salvage' antifungal does not necessarily represent a superior efficacy of the drug.

A clinically stable patient showing no significant deterioration of gas exchange, radiological signs of infection, laboratory parameters etc. has been assessed as clinical non-response in several clinical studies in newly developed systemic antifungals [1,12]. From clinical experience, such a stabilization in a profoundly immunosuppressed patient with IA may indeed represent a fundamental success rather than a failure. If such a patient is switched to another antifungal drug and later shows partial improvement of clinical signs and symptoms, this may inadequately be attributed to the 'salvage' antifungal.

In the most frequent clinical scenario, patients with pulmonary aspergillosis emerging during profound neutropenia will show enlargement of pulmonary infiltrates, eventually accompanied by clinical deterioration (including single cases of hemoptysis), when hematopoietic recovery occurs [13,14]. Whilst this constellation formally fulfills the criteria of antifungal treatment failure justifying the inclusion into a study on the efficacy of a 'salvage' antifungal, it may in fact represent a transient clinical deterioration caused by the rapid recruitment of newly generated neutrophil granulocytes and monocytes to the pulmonary 'battlefield', resulting in a favorable clinical outcome also without changing antifungal treatment [13].

If 'pro-inflammatory' laboratory parameters such as serum C-reactive protein or interleukin-6 are used for the assessment of clinical response, increasing levels or persistently high levels may falsely be taken as indicators of clinical failure, owing to a documented bacterial infection or fever of unknown origin. Persistence of these parameters, however, may in the context of hematopoietic recovery be a signal for an improvement of immune response rather than for non-response.

If persistence of *Aspergillus* spp. in samples taken from a clinically or radiologically identified focus of IA (e. g. resected lung tissue) is unequivocally designated a failure of antifungal treatment, this may as well falsely give reason to assess a clinical course of antifungal treatment as failure. Infarcted tissue, which may represent typical sequelae of invasive pulmonary or cerebral aspergillosis, may contain living filamentous fungi, because this material is only poorly penetrated by an intravenously provided antifungal. This does, however, not indicate a lack of clinical efficacy of this drug against the respective fungal pathogen. While sterilization of infected tissue should be maintained as a goal of antifungal therapy, it might be useful to distinguish a clinical success, e.g. in a patient in whom later on *Aspergillus* spp. can still be diagnosed from resected lung tissue, from microbiological failure.

If IA is treated with an echinocandin such as caspofungin, and the course of *Aspergillus* galactomannan levels in serum does not show a stable decrease, this phenomenon does not necessarily represent non-response to the antifungal, because such a persistence or increase in galactomannan levels may be observed despite successful treatment of aspergillosis [15]. It has been repeatedly shown that concomitant antibiotic therapy with piperacillin-tazobactam or some other semisynthetic beta lactam antibiotics may cause 'false-positive' *Aspergillus* galactomannan levels [16,17]. In such a situation, stating failure of antifungal treatment because of persisting or increasing galactomannan levels would not be appropriate.

Patients primarily treated with amphotericin B deoxycholate or one of the lipid formulations of amphotericin B, who are switched to a 'salvage' antifungal such as caspofungin or posaconazole, will necessarily be treated with a combination therapy of the polyene and the second-line antifungal. The pharmacokinetic properties particularly of the liposomal formulation of amphotericin B result in long-term persistence of high drug concentrations in lung tissue and other sites [18], making the assessment of the clinical efficacy of a polyene given as second-line antifungal therapy extremely vague.

How can a 'salvage' trial in patients with invasive aspergillosis be designed?

Primarily, it should be recommended that in clinical studies on second-line antifungal treatment for IA, patients should separately be evaluated with respect to their reason for 'failure' of primary antifungal treatment. Patients with documented intolerance to a previously given antifungal should be regarded as a population virtually treated 'first-line' with the 'salvage' antifungal.

Another important issue is randomization and blinding of patient allocation to an external data reviewer. Ideally, a three-arm study (continuation of primary antifungal vs. combination of primary antifungal with a 'salvage' drug vs. the 'salvage' drug alone) would be designed. In clinical practice, such a study may be impossible to conduct with respect to the number of patients required and the high associated costs.

It would be important to avoid imbalance of preceding first-line antifungal regimens among patients entering a 'salvage' trial. If sufficiently high numbers of patients are recruited, this aspect may be neglected from a statistical point of view. In other cases, stratification of patients according to their previous antifungal treatment may be recommended. Ideally, the first-line regimen would be standardized.

Host criteria such as neutropenia or extent (and treatment) of graft-versus-host disease should be clearly defined and documented with respect to their course over time, and patients entering a 'salvage' trial for refractory IA should be stratified according to these criteria. The course of neutrophils during 'salvage' antifungal treatment should be documented, because 'neutropenia at study entry' may include two patient subgroups with completely different prognosis, namely

those with persistent profound neutropenia and those who develop hematopoietic recovery.

Patients with an expected short survival may be excluded from 'salvage' trials. If terminally ill patients are included and die under treatment, their causes of death should be critically analyzed with respect to a potential failure of antifungal therapy.

Criteria to define 'clinical refractoriness', 'resistance', 'non-response' or 'failure' respectively should be re-defined. In order to evaluate the clinical usefulness of an antifungal drug, it seems useful to differentiate clinical from microbiological response. One option to establish a valid definition of response would be to use a composite assessment score including (i) clinical as well as (ii) radiological and (iii) microbiological or mycological criteria. The latter may include non-culture based methods such as the sequentially performed serum galactomannan determination. Patients should not be evaluated earlier than after seven days of full-dose systemic antifungal treatment. In individual cases, e.g. a patient with hematopoietic recovery showing increasing volume of pulmonary aspergillosis and clinical deterioration, it may be recommended to continue the current antifungal treatment for another seven days before clinical failure is stated.

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