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Challenges of patient recruitment for invasive aspergillosis trials

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The main challenge in patient recruitment for invasive aspergillosis (IA) trials is to include a maximum number of patients for a minimum length of time, bearing in mind that the final objective is to improve the prognosis of patients with IA. Theoretically, all that is needed is a good drug and a good strategy. The analysis of patient recruitment rates in the most recent important trials of fist line and salvage therapy of IA shows that they are quite low, ranging from two to 18 patients per month, despite high numbers of participating countries and investigators. Several difficulties are encountered: IA is not a frequent disease and inclusion criteria may well exclude patients with true aspergillosis. Competing IA trials and concomitant non IA protocols are often conducted at the same center. Conversely, large numbers of patients (hundreds) are mandatory in the frequently chosen 'non-inferiority' trials. Considering the fact that a significant number of IA cases are not diagnosed premortem, new diagnostic methods should be developed to allow an early diagnosis and thus increase the number of treatable patients. Furthermore, the choice of other endpoints for assessing antifungal activity could decrease the duration of studies and, hopefully, the number of needed patients.

Keywords Aspergillosis, methodology, invasive aspergillosis trials, patient recruitment, accrual

Introduction

The main challenge in patient recruitment for invasive aspergillosis (IA) trials is to include a maximum number of patients for a minimum length of time, bearing in mind that the final objective of such a trial is to improve the prognosis of patients with IA. Theoretically, all that is needed is a good drug and a good strategy. However, recruiting patients has proven to be a difficult task.

The recruitment statistics of five recent important trials of primary ($n=2$) or salvage treatment of IA ($n=4$) show that although the number of approved centers per study was generally large, up to 199 worldwide in the trial comparing voriconazole and amphotericin B in the primary treatment of IA (the so-called Global *Aspergillus* Comparative Study), only half of them were active centers actually enrolling patients [1]. The highest figure was found in the so-called Ambiload trial which compared a liposomal amphotericin B loading dose regimen versus a standard liposomal amphotericin B regimen for the initial treatment of invasive mould infections (mostly IA), where 64% of the centers actively enrolled patients [2]. Centers may encounter difficulties in enrolling patients for a variety of more or less good reasons. A frequent problem is related to the existence of competing trials. There may be, at the same center, several concurrent trials for the treatment of fungal infections or for antifungal prophylaxis. Moreover, there may be some concomitant non antifungal studies that preclude any entry in any other study protocol.

The average number of enrolled patients per month was 9.6 in the Global *Aspergillus* Comparative Study (total study duration: 41 months) and 18.8 in the Ambiload trial (total study duration: 18 months) [1,2]. In the Posaconazole salvage therapy trial the number of

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enrolled patient per month was 4.1 (total study duration: 26 months) [3]; it was 2.11 (total study duration 60 months) and 3.3 (total study duration 16 months) respectively, in the two Caspofungin salvage therapy trials (monotherapy and combination therapy) [4,5]. In these five trials, the average numbers of patients/month/approved center were respectively, .05, .26, .05, .03, and .10. These figures raise three comments: (1) The inclusions are universally slow, (2) Logically, the inclusion of patients in a salvage trial can be expected to be at least twice as slow as in a primary therapy trial because it can be assumed that at least 50% of the patients have either responded to first line therapy or died, which is obviously not the case and, (3) It can be seen that the longer a trial lasts, the slower the rate of inclusions is. This fact is perfectly illustrated in the Global *Aspergillus* Comparative Study where the decrease in inclusion rate was linear overtime. As this trial was an open one, it probably gradually occurred to the investigators that one arm of the study was more advantageous than the other one.

Although IA is a major concern in patients with immunocompromised states, it is not diagnosed very frequently. In this respect, the Transnet data show a surprisingly low incidence of IA of around 15/1000 transplant patients between 2001 and 2002 [6]. At our own hospital, a tertiary care center comprising 600 beds where a third of the patients are immunocompromised, the total number of probable and definite aspergillosis, using previously published criteria has been about 25 for the last 5 years [7]. Using the EORTC-MSG criteria would decrease the number of cases by 30% [8]. Noteworthy, 30% of the patients included the so-called Global *Aspergillus* Comparative Study were so on the basis of radiological findings only [1,9]. In this trial, allogeneic stem cell transplant recipients and neutropenic patients could be included with a diagnosis of probable IA if they had a halo sign or an air crescent sign on lung CT scan. According to the EORTC-MSG criteria these patients would have been classified as having possible disease and therefore would have been excluded from the study, whose duration would have been extended for another year. A secondary analysis demonstrated that the outcome of these patients was the same as that of the whole population of patients and as of the patients with definite IA [9]. As pointed out recently, it may well be that the current European Organisation for the Research and Treatment of Cancer and the Mycosis Study Group (EORTC-MSG) criteria admit only a portion of patients with eventually proven invasive disease [10]. Revised criteria are pending that would allow some very well defined possible cases to meet study case criteria [9,11].

Ways to improve patient recruitment are mandatory. Below are some tracks.

An objective that must be attained is to improve the diagnosis of IA and thus to increase the number of treatable patients and hopefully to increase the cure rate. Indeed, a recent autopsy survey done between 2000 and 2004 has shown that almost 40% of IA cases remain undiagnosed pre-mortem [12]. From this perspective, diagnostic tools (imaging and biological markers) must improve in sensitivity and specificity, and most importantly must be available to every physician in charge of patients.

A thorough real time analysis of screen failures for a given protocol could lead to amendments allowing improved inclusion rates. This has seldom been done.

Innovative strategies can be elaborated. The strategy that was used in the Ambiload trial was innovative and elegant. Patients could be included on the basis of 'possible' invasive mould infection and were allowed to continue in the study if proven or probable invasive infection was confirmed within four working days after study entry. Thirty-eight of the 226 patients (17%) were thus upgraded from possible to probable/definite disease, which in the end saved time [2].

Another way could be to decrease the number of patients that are needed in a trial. For example, 'superiority' trials for efficacy assessment would require significantly few patients that the frequently chosen 'non-inferiority' methodology. One limitation to this consideration is that failure to prove superiority, in a superiority trial, does not allow concluding to non-inferiority. Knowing the fact that most trials depend on funding by pharmaceutical companies, one can easily understand why these companies are not willing to take the chance of such trials. Finally, finding creative endpoints as time to response/progression rather that the percentage of response at a fixed time period, or even better, the use of surrogate markers, would decrease the duration of studies and the number of patients required [13].

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