Salvage therapy for invasive aspergillosis

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Invasive aspergillosis (IA) makes a marked contribution to the mortality of immunocompromised hosts, especially those who have received cytotoxic chemotherapy for haematological malignancy or allogeic haemopoietic stem cell transplantation. Salvage therapy, in the case of invasive fungal infection, generally refers to the treatment of infected individuals who are refractory or intolerant to initial therapy administered for at least 7 days. Although clinical trials of salvage therapy of IA have been undertaken, most were non-comparator studies or contained a non-randomized control group, and criteria for patient enrolment and the methods used to assess response were variable. Salvage therapy has produced relatively disappointing results, emphasizing the importance of early diagnosis and effective primary therapy for IA. Despite this, a number of agents have been studied in the treatment of IA and have demonstrated efficacy in a salvage setting. These include lipid-based formulations of amphotericin B, caspofungin, itraconazole, voriconazole, posaconazole and micafungin. Combinations of echinocandins with either azoles or amphotericin B have also been studied in small series. Further studies are required, ideally comparing newer agents and treatment strategies in randomized clinical trials, to clarify the optimal approach to salvage treatment of IA in this challenging group of patients.

Keywords: antifungal invasive fungal infections, amphotericin B, caspofungin, voriconazole, posaconazole

Introduction

Invasive aspergillosis (IA) is a leading cause of death in immunocompromised patients, in particular those receiving chemotherapy for haematological malignancy or haemopoietic stem cell transplantation (HSCT). Historically, treatment of IA in these groups has been disappointing. This has reflected both the poor prognosis of the underlying conditions, which predispose to IA, and also the limitations of existing antifungal therapy. Recently optimism has increased that response to treatment could be improved for this challenging group of patients.

A variety of treatment strategies for the management of IA have been proposed and target different stages in disease evolution. These include prophylaxis, empirical, pre-emptive [employing radiological screening with high-resolution thoracic computed tomography (CT) in combination with assays such as the galactomannan enzyme immunoassay], primary and salvage therapy.4

Issues relating to study design

Options for salvage therapy have been guided by a number of clinical trials aimed at investigating the impact of particular agents when used as ‘salvage therapy’. Interpretation of these trials hinges on a number of critical aspects of study design. The first of these concerns study entry criteria. Patients in salvage therapy trials include patients both ‘refractory’ and ‘intolerant’ to standard therapy, but individuals enrolled because of intolerance have a much better response rate.5 Also, refractory disease is usually taken to include progression of disease or failure to improve after 1 week (occasionally longer) of therapy, but the exact definition of ‘refractory’ has varied between studies with the result that the patient populations in salvage studies are not always directly comparable.

Criteria employed to define lack of response are variable. Radiological criteria are normally included but it is important to remember how invasive pulmonary aspergillosis evolves with treatment. In studies by Caillot et al.,6 the volume of pulmonary lesions increased 4-fold in the first week and then remained stable during the second week of therapy. Radiologically defined progression may misclassify cases as refractory to primary therapy. Radiological features should thus be combined with clinical features, but the clinical parameters for measuring response are also variable. In patients with neutropenic fever, the majority of individuals will remain febrile for >1 week despite antifungal therapy.7 Similarly, respiratory symptoms may equally be slow to respond to therapy or may not be clearly linked to IA.

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When interpreting existing salvage studies, we have to recognize these limitations and understand that in many cases the individuals enrolled were not ‘failing’ first-line therapy.

To date most salvage studies have been open, non-randomized studies comparing results with historical controls or some other comparison group. Such comparison groups may, however, have important and undefined differences from the group enrolled in the study. Furthermore, the response to therapy in the comparator group may or may not have been subjected to the same vigorous assessment of response. It is imperative, as suggested by Bennett,9 that we now perform randomized clinical trials to properly evaluate salvage therapy for IA.

Outcomes of IA vary greatly by patient group, with patients with allogeneic HSCT often having worse outcomes. Patients enrolled in salvage studies have often comprised heterogeneous groups, resulting in variation in the proportion of poor-outcome groups between studies. Improved study design would result if future salvage studies were limited to defined groups.

A final area of some concern is reporting of outcome. When death is recorded as an endpoint, it is very hard to establish whether the death was related to the invasive fungal infection or due to the underlying disease. Trials need to record as much detail as possible in this regard and present it in a clear and unbiased fashion.

Studies of single agent salvage therapy

**Amphotericin B**

Liposomal amphotericin B is licensed for the salvage treatment of IA and remains the antifungal agent for which most clinical experience exists. Pre-licensing studies of lipid-based formulations of amphotericin B, involving patients with IA who were refractory to or intolerant of existing therapy, demonstrated efficacy of lipid-based formulations in salvage therapy for IA.9 However, these studies included a mix of patients with different fungal infections and different disease stages. The success of liposomal amphotericin B in a salvage setting is based largely on its ability to induce a favourable response to therapy in individuals who are intolerant of amphotericin B deoxycylolate. In an analysis of outcomes in patients with IA randomized to voriconazole or amphotericin B deoxycylolate, lipid-based formulations of amphotericin B induced successful overall salvage in 28% of individuals who originally received amphotericin B deoxycylolate. However, success was seen in only one of eight patients (12%) who received salvage with a lipid-based formulation when refractory to amphotericin B deoxycylolate, and it was apparent that success was much more likely if the reason for the switch was that the patient was originally intolerant, but not refractory, to amphotericin B deoxycylolate.10

**Echinocandins**

The development of the echinocandins paved the way for salvage studies in which a separate class of antifungals could be administered after primary therapy. In a non-comparative multicentre study of 83 patients with IA who received caspofungin as salvage therapy,5 86% of patients were refractory to conventional therapy—mostly amphotericin B in various formulations but also itraconazole. ‘Refractory’ was defined as failure to respond clinically or progression of disease after at least 7 days of therapy. However, in this study 66% of those enrolled had received at least 14 days prior therapy. Forty-eight per cent of the subjects had haematological malignancy and 25% were allogeneic haematopoietic cell recipients (blood or marrow). Responses were evaluated by three experts who assessed the clinical and radiological response at the end of therapy. Treatment duration was variable but was for a mean of 28 days. A favourable response was observed in 44.6% of individuals although a complete response was only obtained in 5%. In this study, 48% of individuals died during the study period and in 12%, IA was believed to be the likely cause of death. The favourable response rate, however, ranged between 39% for those with refractory disease and 75% of those intolerant to prior treatment and was only seen in 14.3% of those with allogeneic haematopoietic cell transplantation. Caspofungin was well tolerated.

A compassionate-use study for caspofungin (which is now licensed for use in salvage therapy of IA) enrolled 48 individuals and was broadly similar except that the assessment of response was solely determined by the study investigators. It also demonstrated a 44% favourable response rate and little toxicity.11 Data on the newer echinocandins are more limited and mostly consist of abstracts to date. An open-label study of micafungin included 22 individuals who received micafungin monotherapy for refractory disease.12 Study design was similar to the caspofungin studies and a favourable response to therapy was seen in 41%.

**Azoles**

Azole therapy has also been used for salvage therapy. Although itraconazole has a license for use in salvage therapy, limited availability of the parenteral formulation, issues concerning the bioavailability of capsules and the greater potency of the newer azoles for aspergillosis have meant that it is less likely to be used in this setting. Voriconazole was superior to amphotericin B deoxycylolate in a randomized multicentre trial of primary therapy for IA13 and is more likely to be employed as primary therapy rather than salvage therapy. This trial was, however, designed as a non-inferiority study and the comparator was not a lipid-based formulation of amphotericin B. In a pre-licensing, open, non-comparative multicentre study of voriconazole in patients with IA,14 56 of 116 patients (48%) were enrolled for salvage therapy. The reason for salvage was not recorded, but the majority were refractory to prior therapy, with amphotericin B (various formulations) or itraconazole administered for at least 10 days prior to enrolment. In the overall group, 58% had haematological malignancy and 20% allogeneic HSCT. Response was assessed by a single expert who evaluated clinical, radiological and mycological outcomes. The individuals received a mean of 12 days of intravenous therapy followed by 77 days of oral therapy. The overall response rate in the salvage group was 38%. Of these, 11% were complete responses. Ninety-day survival in the salvage group was ~40%. Overall outcomes were superior when voriconazole was used as primary therapy rather than salvage therapy. A smaller trial of voriconazole therapy for salvage of invasive fungal infection (largely IA) in a group comprising predominantly transplant recipients (29% solid organ, 24% HSCT) demonstrated a 58% response rate.15

The role of posaconazole as primary therapy for IA awaits clarification. Nevertheless, it has also been studied in salvage
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therapy in a multicentre trial, which contained an external control population.\textsuperscript{16} The control population was collected largely from the same centres that enrolled individuals into the study and largely over the same time period, although 30% of cases were not contemporaneous. The posaconazole-treated group entered into the modified intent-to-treat analysis consisted of 107 patients, of whom 87.8% were refractory to prior therapy as defined in the caspofungin studies above. Prior therapy consisted of amphotericin B preparations, itraconazole and other antifungals with a median period of 23 days of therapy in the refractory group and 12 days in the intolerant group. At enrollment, 74\% had haematological malignancy and 45\% had received allogeneic HSCT. Patients could be treated for up to 372 days with 800 mg of posaconazole suspension per day in 2–4 divided doses. A data review committee assessed all outcomes in the posaconazole-treated group and the external controls and a modified intent-to-treat analysis was performed. A logistic regression analysis determined that the posaconazole-treated group was similar to the external controls. The external controls, all of whom received amphotericin B deoxycholate, lipid-based formulations or itraconazole, received therapy for a median of 22 days as compared with 56 days for posaconazole. Successful response to treatment was observed in 42\% of the posaconazole group and 26\% of the controls with end-of-treatment survival rates of 38\% versus 22\%. Response rates were 37\% for patients with haematological malignancy and 31\% for allogeneic HSCT. Posaconazole was well tolerated with minimal side effects.

Alternative salvage strategies

Salvage therapy of IA has limited success. This emphasizes the need to initiate effective therapy at the earliest opportunity since early diagnosis and treatment improves outcome.\textsuperscript{17,18} It also indicates the need for more effective salvage strategies. Most of the agents discussed have demonstrated efficacy that approximates that of historical studies with amphotericin B, albeit with less toxicity. Newer agents such as voriconazole may improve primary treatment outcomes.\textsuperscript{13,13}

One approach to improve salvage therapy is combination therapy. Marr et al.\textsuperscript{19} examined response rates to the combination of voriconazole and caspofungin. This single-centre, case–control study used the use of voriconazole alone (31 patients) with the combination of caspofungin and voriconazole (16 patients) as salvage therapy for IA after at least 7 days of therapy with amphotericin B. The participants were largely allogeneic HSCT recipients. Overall mortality and death due to IA was significantly greater in the monotherapy group. Other combinations that have been studied in open non-comparative salvage settings, with initially encouraging results, include caspofungin and amphotericin B\textsuperscript{20} and micafungin with various azoles or amphotericin B.\textsuperscript{12} The role of combination therapy clearly merits further investigation.

Other strategies for salvage therapy in IA include surgery in selected cases. Immunomodulation with granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor or interferon-γ have all been described in case reports and small series but their role in salvage requires determination.\textsuperscript{2} Strategies to inhibit the molecular chaperone, heat shock protein 90, either with monoclonal antibody or small molecule inhibitors, may increase the susceptibility of Aspergillus spp, to cell-wall-active agents such as the echinocandins and suggest another intriguing approach to therapy in the future.\textsuperscript{23}

Conclusions

Salvage therapy of IA remains a major challenge. Clearly, early therapy with effective and non-toxic primary treatment will remain essential. In cases that require salvage therapy further studies are needed to evaluate the relative strengths of the newer echinocandins or azoles as compared with lipid-based amphotericin B formulations and to determine the future role of combination therapy or novel agents. With a larger pool of agents to evaluate it now becomes essential that future studies should use standard definitions, homogeneous groups and employ randomization to maximize the quality of the data they generate.

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Transparency declarations

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