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Review Article

Combination Antifungal Therapy for the Treatment of Invasive Aspergillosis: A Review

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Abstract

Invasive aspergillosisis associated with significant morbidity and mortality in the immunocompromised host, and has become a dreaded complication of cytotoxic chemotherapy, hematopoietic stem cell transplantation, solid organ transplantation and other high-risk conditions. Current guidelines recommend monotherapy with voriconazole as the initial treatment of choice for invasive aspergillosis; however, disease progression despite the use of a single agent is relatively common. We need more efficacious and reliable antimicrobial treatment strategies. Given the high mortality associated with invasive mold infections, the proven in vitro synergy between certain antifungals, the safety of echinocandins, and the trend towards improved mortality in both animal and human studies, clinicians must consider dual antifungal therapy with voriconazole and an echinocandin for the severely immunocompromised host with proven infection and a significant disease burden. While combination therapy is currently recommended only for salvage therapy in national guidelines, it may not be prudent to wait for treatment failure before using dual agents. In the scenario of prolonged, severe neutropenia and other profoundly immunocompromising states, I – and many other experts – recommend initial combination therapy with voriconazole and an echinocandin in patients with proven invasive aspergillosis, an opinion with some support in the literature.

Keywords: Aspergillosis; Treatment; Combination; Antifungal

Abbreviations

HSCT: Hematopoietic Stem Cell Transplant; GVHD: Graft-Versus-Host Disease; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society; µg: Micrograms; mL: Milliliter; µL: Microliter; kg: Kilogram; IV: Intravenous; FDA: U.S. Food and Drug Administration; VATS: Video-Assisted Thoracoscopic Surgery; ANC: Absolute Neutrophil Count; CI: Confidence Interval; HR: Hazard Ratio

Introduction

Invasive aspergillosis is a serious opportunistic mold infection associated with very high morbidity and mortality, particularly in the severely neutropenic host after cytotoxic chemotherapy [1-3]. Other risk factors include severe, prolonged neutropenia from any cause, HSCT, GVHD, high-dose glucocorticoid therapy, and solid organ transplantation, especially of the lung. Over time, it has emerged to become a leading infection-related cause of death and a feared pulmonary complication in those undergoing HSCT, with mortality ranging from 30-80% despite treatment, depending upon host factors, antifungal choice, and the extent of disease [4-7]. In any immunocompromised host with invasive aspergillosis, outcomes remain unacceptably poor when applying our current treatment guidelines.

A landmark prospective, randomized, unblinded trial showed voriconazole to be superior to amphotericin B deoxycholate for initial therapy of invasive aspergillosis [8], and it is now the drug of choice (A-I recommendation)in national guidelines of the IDSA and ATS [9,10]. Other studies have also established the importance of including voriconazole in the initial treatment regimen for invasive aspergillosis [11]. However, outcomes using single drug therapy remain poor, with a mortality rate of almost 30% at 12 weeks in the voriconazole arm of the aforementioned prospective trial [8]. Because of the poor prognosis associated with invasive aspergillosis, even despite voriconazole, we need more effective therapeutic strategies, including the optimization of antimicrobial agent choice, dosing and drug monitoring. Certainly, some of the mortality risk cannot be overcome without re-establishing a patient's immune function, and severe immunocompromise is a risk factor for progression and treatment failure. However, barring the ability to more effectively improve neutrophil number and function, we must rely on antimicrobial strategies, and give consideration to the use of combination antifungal therapy.

Due to the relative rarity of mold infections, and the need for multicenter trials, it has been difficult to perform high-quality studies regarding the optimal antifungal treatment of invasive aspergillosis. In addition, published studies have shown somewhat conflicting results, even for similar combination therapies. Because of these factors, the use of dual antifungal therapy remains a point of debate amongst experts. Efficacy data for several combinations have been reported, but voriconazole administered with an echinocandin, such as caspofungin, micafungin or anidulafungin, has been best established.

Current guidelines

Monotherapy with voriconazole is currently recommended as

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the initial treatment of choice of invasive aspergillosis by the IDSA and ATS, having been shown to have superior efficacy and fewer toxicities when compared to amphotericin B [8-10]. Voriconazole has excellent *in vitro* activity against *Aspergillus* species, inhibiting 14-α-demethylation of lanosterol in the ergosterol biosynthesis pathway. With voriconazole, drug monitoring and dose optimization are vital. Up to one quarter of neutropenic hosts being treated with standard doses of oral voriconazole will have subtherapeutic, or even undetectable, levels [11]. Despite the excellent oral bioavailability, several factors can contribute to widely variable serum drug levels, including: the non-linear pharmacokinetics of voriconazole, route of administration (IV versus oral), common drug-drug interactions (including some chemotherapeutic agents and immunosuppressants), hepatic function, age, and the presence of genetic polymorphisms affecting CYP2C19-mediated metabolism [12]. Doses should be optimized based upon voriconazole trough levels on stable therapy, with a goal between 1.5 and 5.5μg/mL, in order to maximize clinical response and minimize adverse effects. However, levels should only be drawn after at least 5-7 days of therapy, and it may take several days before results are available, making it difficult to adjust voriconazole dosing in real-time and without a significant delay. Therefore, despite its *in vitro* activity, reaching adequate and stable serum drug levels to optimize therapeutic efficacy may be a difficult goal to achieve with voriconazole monotherapy, which may account for some of the treatment failures seen in studies and clinical practice.

Other single agents and salvage therapy

Other antifungals with *in vitro* and clinically useful activity against *Aspergillus* species include: amphotericin B deoxycholate and its lipid forms, echinocandins, and other extended-spectrum triazoles such asitraconazole and posaconazole. These alternative antifungals are typically reserved for salvage therapy, either as single agents or in combination, when disease is progressing despite the administration of voriconazole. In general, at least 14 days of stable primary treatment should be given without improvement, or with clinical progression, before refractory infection is declared and salvage therapy is considered. None of these agents can be recommended as primary monotherapy of invasive aspergillosis, but may be beneficial for use in certain cases.

Amphotericin B and its lipid formulations are polyenes which act by binding ergosterol, destroying the structural integrity of the cell membrane through the formation of ion channels – and likely causing oxidative damage – leading to fungal cell death. Polyenes can be difficult to administer due to infusion reactions (fevers, rigors, myalgias, arthralgias, bronchospasm and neurotoxicity), nephrotoxicity and electrolyte disturbances. The advantages of using lipid formulations of amphotericin B include improved patient tolerability and less toxicity, allowing for the administration of higher doses with a lower risk of adverse effects. The standard dosing for amphotericin B deoxycholate is 1 mg/kg IV every 24 hours, and lipid formulations should be given at 5 mg/kg IV every 24 hours. A small, observational study suggested improved outcomes with higher dosing of liposomal amphotericin B, up to 10 mg/kg IV every 24 hours [13]; however, a double-blind trial showed no significant clinical benefits of such high doses along with added nephrotoxicity [14], making it difficult to recommend increased daily polyene dosing. Amphotericin B and its lipid formulations were previously the agents of choice for treating invasive aspergillosis, but have been replaced by voriconazole. Of note, *A. terreus* is often resistant to amphotericin B, but susceptible to sometriazoles, such as voriconazole.

The available echinocandins include caspofungin, micafungin and anidulafungin, and are administered only intravenously. They are very active *in vitro* against most *Aspergillus* species, and work by inhibiting the synthesis of β–(1,3)-D-glucan in the cell wall of fungal pathogens. Of these, only caspofungin is FDA-approved for salvage therapy of invasive aspergillosis, but many experts use the echinocandins interchangeably for the treatment of invasive molds [15]. Echinocandins may be effective for salvage therapy of refractory disease [16], but are generally avoided as single agents.

Similar to voriconazole, other mold-active triazoles can have significant variability in bioavailability from the gastrointestinal tract. One should be mindful of administering these antifungals appropriately, for example: itraconazole capsules (acidic beverage, avoid medications to suppress stomach acid), itraconazole suspension (empty stomach) and posaconazole suspension (high-fat meal). Posaconazole is a broad-spectrum triazole with excellent *in vitro* activity against several molds. It is FDA-approved for prophylaxis to prevent invasive mold infections in those with prolonged neutropenia or graft-versus host disease [17]. It appears to be a very effective triazole when used for the treatment of active disease [18], but does not carry an indication for primary monotherapy at this time. Many have expressed concerns about variable absorption with oral administration of the suspension, limiting its use somewhat in the past. Recently, posaconazole delayed-release tablets and a form for injection became available, providing much more stable, predictable, and reliable drug levels [19]. An open-label study of posaconazole in those intolerant of conventional therapy suggest that it may be a reasonable option, particularly for salvage therapy; however, further study is needed, including trials to elucidate the appropriate dosing and frequency of drug monitoring, before it can be recommended with confidence [20]. Fluconazole does not have significant anti-mold activity and should not be used in the treatment of invasive aspergillosis.

Combination Therapy

The use of multiple antifungal agents in tandem has been evaluated by several investigators for the treatment of invasive aspergillosis, both as initial and salvage therapy. Clinical studies of varying quality have shown conflicting results, with survival benefits reported in some published manuscripts. Many experts in the field have favored dual therapy for several years, given the poor outcomes when using monotherapy, combined with the theoretical advantage of administering agents with different mechanisms of action. Studies have shown varying results, depending on the combination used.

Voriconazole and an echinocandin

Clearly, voriconazole is an essential component of the initial therapy of invasive aspergillosis. Compared to amphotericin B deoxycholate, the longstanding drug of choice, voriconazole is associated with improved responses, lower mortality, fewer side effects, and less toxicity [8]. However, the question arises: Given the high risk of progression and mortality despite monotherapy, could some patients with invasive aspergillosis benefit from the addition

of another antifungal agent? Several *in vitro* studies and animal models have shown synergy, significantly reduced colony counts, and improved survival times when voriconazole was combined with an echinocandin [21-23], providing a basis for studying this combination in humans.

The results of a randomized, double-blind, multicenter study of combination therapy with voriconazole plus anidulafungin were reported in 2012 [24] and the investigators found a trend towards lower all-cause mortality at week 6 of treatment (19.3% in the combination group, 27.5% in the monotherapy group; 95% CI -19.0 to 1.5;$P = 0.09$). While there was not a statistically significant difference, combination therapy was only given for "at least 2 weeks," which is likely not an adequate duration of dual antifungal treatment. In addition, it is doubtful that the study was powered to find a true mortality difference at 6 weeks between these two treatment arms. In the same trial, there was a significantly lower mortality in the combination therapy group amongst those with "probable" invasive aspergillosis, based on a positive galactomannan antigen (15.75 versus 27.3%; 95% CI -22.7 to -0.4; p <0.05).The appropriate duration of combination therapy is unclear. One small salvage study using a polyene and echinocandin showed that a duration of combination therapy of up to 14 days was significantly associated with treatment failure ($P = 0.01$), although it is difficult to apply this finding universally [25]. One would suspect that combination therapy should be administered at least until disease regression, clinical improvement, and perhaps resolution of neutropenia (ANC greater than 500 cells/μL).

Extrapolating the findings of salvage studies may also be useful to some extent. Marr and colleagues evaluated the combination of voriconazole and caspofungin for the treatment of patients who failed initial therapy with amphotericin B [26]. The combination of voriconazole and caspofungin was associated with significantly improved 3-month survival when compared to the voriconazole monotherapy arm (HR, 0.43; $P = 0.048$), including a multivariable model to account for other prognostic variables (HR, 0.28; $P = 0.011$). Other investigators reported that the combination of voriconazole and caspofungin was associated with significantly improved 90-day survival in some subsets of patients with refractory disease, including those with renal failure and when infection was caused by *A. fumigatus* complex, the most common *Aspergillus* species to cause human infection [27]. One frequently-cited retrospective study showed no difference in clinical outcomes between patients receiving voriconazole monotherapy versus combination therapy with an echinocandin [28], but only 33 patients were treated with dual antifungals, and the study was clearly not powered to show a difference between these two groups.

Amphotericin B and an echinocandin

While amphotericin B, and its lipid formulations, remain an option for treating invasive aspergillosis, polyene monotherapy appears have inferior efficacy when compared to voriconazole, and well-established toxicities. Although it may be a less appealing drug than voriconazole for several reasons, some investigators have performed small, uncontrolled studies of combining liposomal amphotericin B with caspofungin for salvage therapy. Patients receiving combination therapy did have more favorable responses in one pilot study using the combination of a polyene and echinocandin [29] and other studies show similar, but not definitive, benefits [25,30]. We do not have enough evidence in the literature to recommend this combination, particularly given the side effects and toxicities associated with the use of amphotericin B. A potentially advantageous scenario for using a polyene-containing combination would be when a clinician is including amphotericin B empirically to treat other invasive molds (e.g. *Zygomycetes*) before a definitive diagnosis is made. Again, these are small, retrospective studies of this combination for salvage therapy, and the results should be viewed with some sense of caution.

Amphotericin B and a triazole

There are no high-quality clinical data to support the use of combination therapy with a polyene and triazole. In fact, studies have shown statistically significant antagonism between these drug classes with no clinical outcomes benefit [31,32]. The mechanism of antagonism is unclear, but there appears to be no adverse pharmacokinetic interaction. It is possible that triazole inhibition of the ergosterol synthetic pathway results in a reduction of amphotericin B binding to fungal cell membranes, although other mechanisms have been proposed. Whatever the mechanism, we do have reasonable data to support avoiding this combination for treating invasive mold infections and these antifungal classes cannot be recommended together.

Adjunctive therapies

Immunomodulation, such as the reversal of neutropenia or reduction of immunosuppressive medications as feasible, can be a vital component of treating invasive mold infections. Clearly, ongoing immune dysfunction leads to a higher risk of disease progression and death [9,12,33]. Studies regarding the use of colony-stimulating factors in neutropenic hosts have shown improvements in neutrophil oxidative burst and damage to *Aspergillus* hyphae [34]; however, we do not have high-quality, randomized data to recommend the universal use of either colony-stimulating factors (such as G-CSF or GM-CSF) or granulocyte transfusions at this time. The clinician must consider the risk-to-benefit ratio of such therapies while we await prospective, randomized trials.

Adjunctive surgical debridement of infected tissue is often considered when treating invasive mold infections. Resection can be complicated by the presence of cytopenias, particularly thrombocytopenia, and comorbidities affecting post-operative outcomes. The role of surgery is not well-defined. It is clearly not necessary in all cases, particularly those with disseminated disease, but resection can be curative if tissue invasion is localized [35] and is essential if severe invasive rhinosinusitis is present [36,37]. The risks and benefits must be weighed on a case-by-case basis. Aggressive platelet transfusions combined with minimally invasive surgical methods, such as VATS, may improve operative morbidity and mortality.

Conclusion

Despite the fact that several *in vitro* studies, animal models, and clinical trials suggest a potential survival benefit, the use of combination therapy remains controversial. This is with good reason, as we do not have definitive patient-based data from high-quality, well-powered, randomized, controlled trials. In addition, the cost

of administering an echinocandin, including medication expenses, placing IV access, maintaining IV access, pharmacy processing and nursing costs, must be factored in to the decision to use combination therapy. Given the high risk of disease progression and mortality associated with monotherapy of invasive aspergillosis, the excellent tolerability and low toxicity of echinocandins, as well as the evidence supporting the use of dual antifungal therapy, I recommend the use of voriconazole with an echinocandin as initial therapy in severely immunocompromised hosts (e.g. ANC less than 100 cells/μL for greater than 7 days) with proven invasive aspergillosis.

While many experts, as well as the IDSA guidelines published in 2008 [9], continue to recommend monotherapy with voriconazole, it is notable that more evidence has become available since the latest consensus recommendations were written, data which show a trend towards lower mortality when combination therapy is used [25]. Delaying the use of combination antifungals for salvage therapy, allowing the invasive mold infection more time to progress, seems to be imprudent. The highly variable metabolism and serum levels of voriconazole, as well as the possibility of triazole-resistant isolates causing clinical disease [38], seem to support the use of two antifungals initially as well. Echinocandins tend to be very well tolerated with few toxicities or drug-drug interactions [39]. Certainly, the decision should be made on a case-by-case basis.

More prospective trials should be undertaken, including cost effectiveness analyses, and perhaps stratifying patients based on the risk of mortality based on other underlying co-morbid conditions. Although dosing is seemingly standardized, the activity of echinocandins is concentration dependent [40] and some investigators suggest that higher doses may be beneficial, and are well tolerated [41]. In addition, we need to optimize methods of prevention, such as appropriate antifungal prophylaxis in high-risk immunocompromised hosts as well as environmental exposures. While it is not definitively beneficial, the use of combination antifungal therapy for some severely immunocompromised patients with invasive aspergillosis remains promising. We have more work ahead to improve outcomes beyond our current gold standards for therapy.

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