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REVIEW

Application of caspofungin in China compared with amphotericin B and fluconazole

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Abstract: Fungal infection has increased in the past 2 decades in China. There are three classes of antifungal drugs, polyenes, azoles, and echinocandins, that are applied frequently in China. Caspofungin, which disrupts the fungal cell wall glucan formation through inhibiting the enzyme 1,3-β-glucan synthase, is one of the echinocandins. According to the results of clinical practices applied in China, caspofungin has shown to be superior to the other two classes of antifungal drugs, due to its efficacy in treating fungal infection (15% superior to fluconazole); fewer adverse events such as infusion-related reaction, hepatic dysfunction, and vomiting (25%–50% lower incidence rate); rapid resolution of symptoms (about 3 days quicker than amphotericin B); and absence of antagonism in combination with other antifungal drugs. However, caspofungin will remain as a second-line antifungal drug in the near future because of its high price and the policy of health insurance reimbursement in China.

Keywords: fungal infection, caspofungin, efficacy, adverse event

Introduction

The past 2 decades have witnessed a steady increase in the incidence of fungal infections due to the application of immunosuppressants and broad-spectrum antibiotics in China.[1,2] Fungal infections are frequently observed in immunocompromised patients. These include patients who have acquired immunodeficiency syndrome (AIDS), those receiving chemotherapy with malignancies and hematologic diseases, and those with other serious underlying illnesses.[3–5] *Candida* and invasive aspergillosis, which are typical fungi, are responsible for serious levels of morbidity and mortality. It is reported that the mortality rate of invasive aspergillosis infection is >30% in China, similar with other countries and districts.[6–8]

More and more Chinese physicians and health care managers are paying attention to the treatment of fungal infection. Although there is good progress in treating fungal infection, challenges still exist. First of all, much research has shown that 8%–15% of nosocomial infections were attributed primarily to fungal infection.[9] *Candida* and invasive aspergillosis were most common.[10] There are cases showing *Candida* and invasive aspergillosis resistant to amphotericin B and azole derivatives.[11–13] Secondly, there is no gold rule to diagnose fungal infection, due to the immature fungal diagnosis method. As a result, the reported incidence of fungal infection is lower than the real incidence, the dangers of fungal infection are not realized by many physicians, and empirical therapy is adopted without laboratory diagnosis.[14,15] Thirdly, the incidence of fungal infection has increased rapidly and is ahead of the speed of the research of diagnosis and treatment.[16] Twenty percent to 40% of patients have undergone organ transplant and 90% of AIDS patients were infected by fungi.[9]

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The current treatment options for fungal infections

There are three classes of antifungal drugs, polyenes, azoles, and echinocandins, that are most frequently used worldwide nowadays (Table 1).

Polyene, eg, amphotericin B, has potent antifungal action and broad antifungal activity against the majority of yeasts, including *Candida* and molds, through changing the permeability of the fungal cell wall. There are reports that the effective rate of amphotericin B in treating invasive fungal infection was about 60%. There were no significant changes in serum creatinine and potassium levels.[17] However, amphotericin B in treating fungal infection is not the first choice, due to its severe adverse events, such as nephrotoxicity, infusion-related reaction, fever, and vomiting.[18–20] Amphotericin B is demonstrated to be poorly tolerated. It is difficult to administer for a sufficiently long duration.

Azoles such as itraconazole, voriconazole, fluconazole, and posaconazole are the main triazole antifungal drugs that inhibit the enzyme lanosterol demethylase by blocking the biosynthesis of ergosterol.[21] Fluconazole is used as a first-line therapy for *Candida*, which is responsible for 80% of nosocomial fungal infection. However, the number of susceptible species that are resistant to azoles is increasing due to their extensive use.[22,23]

Echinocandins include caspofungin, micafungin, and anidulafungin. These antifungi inhibit the enzyme 1,3-β-glucan synthase, then result in disruption of cell wall glucan formation.[24] Caspofungin is indicated for the treatment of *Candida* and invasive aspergillosis. Micafugin does well in treating *Candida*. Anidulafugin is an antifungal drug for the majority of *Candida*, including those with resistance to fluconazole. Compared with the other two classes of antifungal drugs, echinocandins have a broader spectrum of antifungal activity and fewer adverse events. There are reports that the incidence of liver and kidney dysfunction was 3.8%, which is significantly lower than that of amphotericin B (13.4%), when treating invasive aspergillosis in an aged population.[25,26] Meanwhile, echinocandins offer relatively rapid resolution of symptoms but fewer or negligible interactions with other drugs.[27,28]

Pharmacology of caspofungin

Caspofungin is one of the echinocandin antifungal drugs, with a mechanism of action that targets a structural component of the fungal cell wall. Caspofungin is an inhibitor of 1,3-β-glucan synthesis, which is a structural component of the fungal cell wall responsible for maintaining integrity and rigidity but is absent from mammalian cells.[29,30] When 1,3-β-glucan synthesis of a fungal cell wall is inhibited by caspofungin, the cellular contents will balloon out from the weakened cell wall because of the high osmotic pressure of the protoplast. The lysis of the cell will happen consequently.[31]

Poor absorption after oral administration (<0.2%) limits use to the intravenous route. After intravenous injection, caspofungin highly binds with protein (about 96%). Caspofungin is widely distributed in the body and is metabolized by the liver. It is degraded mainly in the liver by hydrolysis and N-acetylation, and a small part of it is also degraded in the adrenals and spleen.[32,33] The slow phase of degradation leads to a long terminal half-life. As a result, the β-phase half-life is 9–10 hours.[34] Spontaneous chemical degradation can be observed in caspofungin. It is reported that the average plasma clearance rate was about 10–12 mL/min.[35] Results of radiolabel studies suggested that 35% of degradation products were in the bile and excreted through feces, 41% of those were excreted through urine, and only about 1.4% of residual drugs were excreted through urine without degradation.[36] It can be concluded from the radiolabel result that the liver is the most important metabolic organ for caspofungin, although some of the degradation products are excreted through skin.[37] Plasma concentrations of caspofungin will slightly increase when renal failure patients are exposed to caspofungin. This phenomenon has nothing to do with renal excretion or

Table 1 The characteristics of the three main classes of antifungal drugs

Type	Typical drugs	Pharmacology	Good points	Shortcoming
Polyenes	Amphotericin B	Change the permeability of the fungal cell wall	High effective rate of treating invasive fungal infection	Severe adverse reaction
Azoles	Itraconazole, voriconazole, fluconazole, posaconazole	Inhibit the enzyme lanosterol demethylase by blocking the biosynthesis of ergosterol	High effective rate of treating *Candida*	Resistance
Echinocandins	Caspofungin, micafungin, anidulafungin	Disrupt the cell wall formation in fungi by inhibiting the enzyme 1,3-β-glucan synthase	Broader spectrum of antifungal activity, fewer adverse effects, rapid resolution of symptoms, fewer interactions	Expensive

plasma protein binding.[38,39] For severe hepatic dysfunction patients, it is recommended that dosage should be reduced to 50% daily dose after a standard loading dose, although this recommendation is not backed by clinical data.[40,41] Although when compared with young patients plasma concentrations of caspofungin in the aged patients increase slightly due to slower metabolism, dosage alteration is not needed.[42]

For caspofungin, drug interactions are few. A liver enzyme inducer will accelerate the metabolism of caspofungin in the liver, resulting in the decreased plasma concentration of caspofungin. Caspofungin and cyclosporin are documented interactions, resulting in raised plasma concentrations of caspofungin. There is no report about interaction with other antifungal drugs such as itraconazole and amphotericin B.[43,44]

The application of caspofungin in Chinese patients

Fungal infections are frequently observed in immunocompromised patients, as mentioned. The majority of fungal infections are caused by *Candida* and refractory invasive aspergillosis. Caspofungin is the first echinocandin antifungal drug. Although there is no caspofungin made in China, its efficacy has been witnessed in clinical practice in China.

According to the Chinese guidelines for fungal infection treatment for immunocompromised patients, caspofungin is recommended to prevent invasive fungal infection until the status of immunocompromised alleviates. The prevention dosage is 50 mg per day. For those patients who are proved to be infected by *Candida* through the blood culture results or who cannot tolerate other classes of antifungal drugs, when severe adverse events appear, caspofungin will be applied. As with other countries, the loading dosage is 70 mg, followed by 50 mg daily. Only in moderate or severe hepatic dysfunction patients should caspofungin need be decreased to 35 mg.[9,45]

The efficacy, safety, and tolerability of caspofungin in Chinese patients

There is a clinical study where caspofungin was compared with fluconazole to evaluate its efficacy, safety, and tolerability in China. Thirty-six patients with systemic fungal infections in an intensive care unit were randomly assigned to receive caspofungin or fluconazole. The caspofungin group, which had 18 patients, was treated with caspofungin for 14 days (70 mg loading dose, followed by 50 mg daily). The fluconazole group, which also had 18 patients, was treated with 50 mg fluconazole daily for the whole 14 days. Efficacy and adverse events in the two groups were observed. The effective rate was 100% in the caspofungin group and 66.7% in the fluconazole group. The incidence rate of adverse events in the caspofungin group was 22.2%, while it was 72.2% in the fluconazole group. There were significant differences in the effective rates between the two groups ($P<0.05$), and the incidence rate of adverse events in the caspofungin group was significantly lower than that in the fluconazole group ($P<0.05$). This result suggested that caspofungin was superior to fluconazole in both efficacy and safety in the treatment of severe pulmonary fungal infection in an intensive care unit.[46]

Another comparative study of caspofungin and amphotericin B deoxycholate in invasive fungal infections was also conducted in hematologic malignancy patients. A total of 68 cases of hematologic malignancy patients had secondary invasive fungal infection. They were divided into two groups. Group 1, which had 35 patients, received amphotericin B treatment only (5 mg loading dose with an additional 5 mg daily the following day), while group 2, which had 33 patients, was given an intravenous injection of caspofungin (70 mg loading dose, followed by 50 mg daily), followed by oral administration of intraconazole. Clinical symptoms (such as fever) in group 1, when treated with amphotericin B, disappeared slowly. The average time that obvious efficacy could be observed in the amphotericin B group was 7–10 days. The process of efficacy appearance of the caspofungin group (3–7 days) was quicker than in the amphotericin B group. Of a total of 35 cases in the amphotericin B group, 25 cases were effective, with the total effective rate of 71.42%, and 25 of 33 cases in the caspofungin group were effective, with the effective rate of 75.75%. Both of the two groups showed good clinical efficacy, and there was no significant difference between those two groups. However, the incidence of adverse effects in the amphotericin B group was significantly higher than in the caspofungin group. The incidence of infusion-related reactions was 31.43% in the amphotericin B group and 6.06% in the caspofungin group. The incidence of damage to liver and renal function was 51.43% in the amphotericin B group and 18.18% in the caspofungin group. The incidence of serious hypokalemia was 60% in the amphotericin B group and 9.09% in the caspofungin group. There was no patient withdrawal until the whole treatment course was completed.[47]

There is also research about caspofungin carried out in aged patients. A total of 50 aged patients (all of them aged >80 years) were diagnosed with invasive fungal disease, including 16 laboratory-confirmed cases, 18 clinic-confirmed cases, and 16 probable cases. Forty-one of them were given caspofungin and nine of them were given fluconazole for 2–9 days, then turned to caspofungin due to poor improvement. The majority of those patients were given a 70 mg loading dose

then 50 mg daily, except two patients who were found to have hepatic dysfunction before treatment and who were given a 70 mg loading dose, which was then reduced to 35 mg per day. The whole treatment course was 2–79 days. The average treatment course was 17.5±15.8 days. The average effective rate was 74%. The average effective rate for those nine patients who were treated with caspofungin substituted for fluconazole was 66.7%. Common adverse events such as chills, fever, headache, nausea, vomit, and diarrhea were not observed. However, liver damage could be observed in the treatment course. Only five patients showed the advent of liver damage or aggravation of liver damage. One of the five patients was found to have a liver disorder before treatment. On the 26th day after treatment, liver damage appeared. On the 34th day after treatment, the basic disease was aggravated and the patient died from respiratory failure. The hepatic function of the remaining four patients continued aggravating, even though use of caspofungin was stopped. This result suggests that there is no significant relationship between caspofungin and liver damage that appeared in the course of treatment with caspofungin. Although one patient withdrew due to decreasing neutrophils, the others adhered to the whole treatment course.[48]

Patient-focused perspectives

Like other countries, the most commonly reported adverse events with caspofungin in China have included fever, infusion-related reaction, headache, nausea, elevation in liver transaminase levels, and histamine-type reaction.[49,50] Although those adverse events exist, physicians clearly know how to avoid or reduce those adverse events. Caspofungin has shown high efficacy of treating the majority of fungal infections, especially those resistant to common antifungal drugs. In total, patients usually adhere to the whole treatment. According to a multicenter observational study in which caspofungin was applied to treat postsolid organ transplant invasive fungal disease in China, Germany, Italy, and the UK, no serious drug-related adverse events were reported and caspofungin was well tolerated as caspofungin monotherapy or as combination therapy with other antifungal drugs.[51] However, caspofungin is still not included in the list of health insurance reimbursements in most provinces of China. This means that patients pay by out-of-pocket if they want to use caspofungin. Due to its high price, caspofungin is still not used widely in China. It will be applied when the other two classes of antifungal drugs are proved useless or severe liver damage appears.

Conclusion

Fungal infection has attracted the attention of Chinese physicians. It is more frequently reported that the traditional antifungal drugs such as fluconazole and amphotericin B are resistant to fungal infection or have more adverse events, while caspofungin showed equivalent efficacy in treating fungal infection in Chinese clinical practice. The absence of antagonism and substantially fewer toxic effects in combination with other antifungal drugs will result in its broad use in the near future. Considering its high price, combination antifungal therapy could become a general feature for caspofungin.

Disclosure

The authors report no conflicts of interest in this work.

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