【Review】

Overview of micafungin (MCFG)

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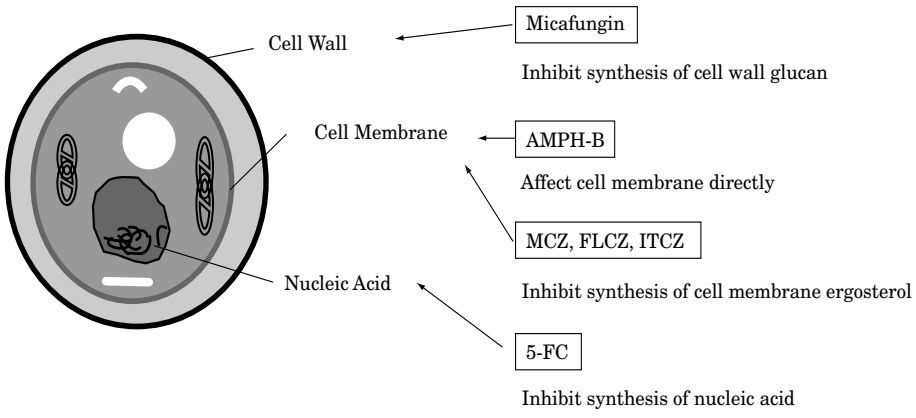
Key words: micafungin, MCFG, overview

Deep–seated mycosis is in most cases a serious disease, with rapid exacerbation and poor prognosis. The diagnosis and treatment of the disease are generally considered difficult. In Japan, the following 5 antifungal agents are currently available: the polyene macrolide antibiotic amphotericin B (AMPH–B), the pyrimidine derivative flucytosine (5–FC), the imidazole antifungal agent miconazole (MCZ), and the triazoles fluconazole (FLCZ) and itraconazole (ITCZ). Of these, only 3, that is, AMPH–B, MCZ and FLCZ, are available as injections. AMPH–B is the preferred agent due to its potency and the spectrum of its antifungal activity, and is widely used in clinical practice for the treatment of deep–seated mycoses. However, this agent, in the therapeutic dose range, has the disadvantage that it can produce various adverse reactions, including severe renal function impairment. As for azole antifungal agents such as MCZ and FLCZ, their extensive use led to the development of azole resistance in *Candida* species[1]. In view of these difficulties, there is a need for a novel antifungal agent with greater clinical utility. Researchers focused on 1, 3–β–D–glucan, a key component of the fungal cell wall, which is not present in the human cells, and tried to develop an agent that specifically inhibits the biosynthesis of 1, 3–β–D–glucan. As a result, micafungin (MCFG), a novel antifungal agent with activity against major causative fungi of deep–seated mycoses such as *Candida* and *Aspergillus*, has been developed (Fig. 1). Candins are a family of antifungal agents that act to inhibit the biosynthesis of cell wall glucan. MCFG, the first candin antifungal drug developed in Japan, has a good safety profile and has a significant therapeutic effect against deep–seated mycoses caused by *Candida* or *Aspergillus*, the major pathogenic fungi. In addition, MCFG is effective against fungi resistant to conventional antifungal agents because of its novel mechanism of action.

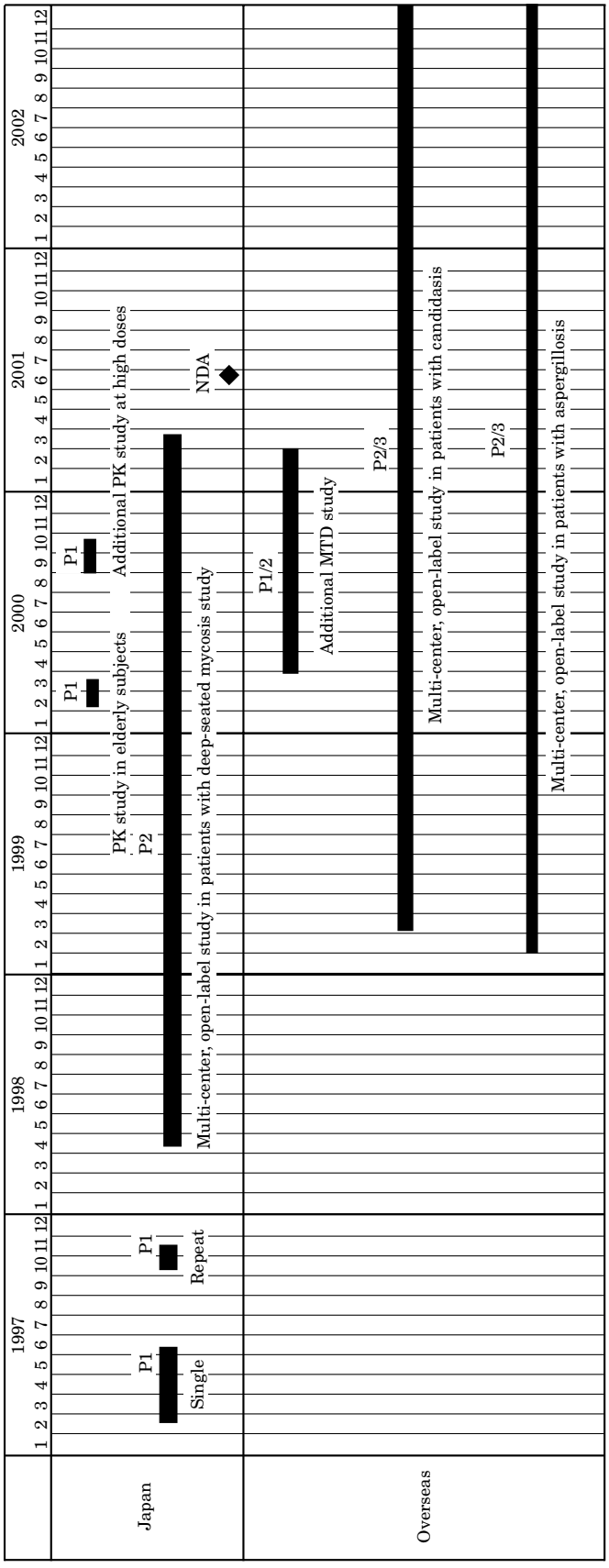
In Japan, the development of MCFG was undertaken in 1995. Phase Ⅰ studies were conducted in 1997 and phase Ⅱ clinical trials started in 1998. MCFG was applied for manufacturing approval in Japan in June 2001. The formal NDA approval was obtained in October 2002 in Japan. At present, the development of this agent is ongoing in other countries (Table 1).



AMPH-B: amphotericin B, MCZ: miconazole, FLCZ: fluconazole, ITCZ: itraconazole, 5-FC: flucytosine

Fig. 1. Mechanism of action of antifungal drugs.

Table 1. Schedule of clinial development of micafungin (main studies)



The current special issue includes the results of pharmacological and pharmacokinetics studies and phase I studies of MCFG conducted in Japan. This article describes a summary of these studies.

MCFG acts against *Candida* and *Aspergillus*, the major causative fungi of deep–seated mycoses, by inhibiting the biosynthesis of 1, 3–β–D–glucan, a major and specific component of the fungal cell wall. This agent proved to have more potent activity than AMPH–B, FLCZ and ITCZ against these pathogenic fungi, except for some species of *Candida*. In addition, MCFG was shown to have excellent antifungal activity against *Candida* that is resistant or poorly susceptible to FLCZ, and shown to have fungicidal activity against many *Candida* species. MCFG was shown to inhibit the germination and hyphal growth of *Aspergillus fumigatus*, although unlike AMPH–B, it did not show apparent fungicidal activity against this fungus. Consistent with the above *in vitro* antifungal features, MCFG significantly prolonged survival in mouse models of pulmonary infection with *A. fumigatus* and disseminated infection with *Candica albicans* at doses of 0.5 and 0.125 mg/kg, respectively. The minimum effective plasma concentrations of MCFG to produce a significant reduction in viable cell count in the target organ ranged from 0.55 to 0.80 μg/mL for the lung and from 0.16 to 0.26 μg/mL for the kidney. For the protective effect evaluated in various mouse models of infection with *Candida* species and *A. fumigatus*, MCFG was more potent than FLCZ and ITCZ and comparable with AMPH–B. MCFG produced not antagonistic but synergistic effects against *C. albicans* and *A. fumigatus in vitro* when combined with either of AMPH–B, FLCZ or ITCZ and showed an excellent synergistic effect *in vivo* with AMPH–B in a mouse model of pulmonary infection with *A. fumigatus*.

After intravenous administration of ^{14}C–MCFG at a dose of 1 mg/kg to rats, isotope–labeled drug was extensively distributed in various tissues. At 5 min, isotope–labeled drug concentrations higher than those in the plasma were observed in the lung and kidney (1.86 and 1.09 times higher, respectively). Isotope–labeled drug was very poorly transferred into the brain (0.02 times plasma concentration). These results indicate the favorable transfer of the drug into organs primarily involved in mycoses. At least 6 metabolites have been observed in the rat and the dog. The major route of excretion was via the bile (feces). After intravenous administration at a single dose of 1 mg/kg to mice, rats and dogs, MCFG was eliminated from the plasma with a half–life of 4.6 to 5.3 hours. Plasma drug concentrations showed dose dependency.

An *in vitro* study using human hepatic microsomes demonstrated that MCFG slightly inhibited CYP 3 A. The degree of inhibition was similar to that by FLCZ. At plasma unbound drug concentrations produced by clinical doses, MCFG was found not to significantly affect the drug–metabolizing activity of the enzyme.

In phase I studies, in which MCFG was administered to healthy adult male subjects at single dose ranging from 2.5 to 50 mg and at multiple dose of 25 mg, the agent was well tolerated. In a single administration study, mean plasma concentration of unchanged drug declined in a bi–exponential manner with a terminal elimination half–life of 11.6 to 15.2 hours. There were no differences among dose group in elimination half–life, volume of distribution at steady –state and total clearance. Maximum plasma concentration increased in proportion to dose. Consequently, the pharmacokinetics of MCFG were considered to be linear over the dose range studied. In a multiple administration study (25 mg/day once daily for 7 days), plasma unchanged drug concentrations reached steady state by the fourth day of administration. Later, another pharmacokinetic study was conducted at higher doses in healthy adult male subjects because the intended clinical dose was increased. The results of the high–dose study, in which MCFG was administered at single doses of 25, 50, 75 and 150 mg and at a multiple dose of 75 mg/day, were similar to those of the phase I studies. Comparison of the pharmacokinetics of MCFG in elderly and non–elderly subjects demonstrated no differences in pharmacokinetic parameters.

One report has concluded that MCFG can be considered effective against candidiasis and aspergillosis, based on the results of clinical studies conducted in Japan and other countries (Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2001); however the report is not included in the current special issue. MCFG was also shown to be effective in patients who failed to respond to conventional antifungal agents, as well as being effective against infectious diseases caused by azole antifungal–resistant *Candida*. With respect to safety, no significant adverse reactions such as AMPH–B associated renal impairment were observed with

MCFG. In a maximum tolerated dose (MTD) study conducted overseas, MCFG did not reach an MTD after administration at a dose of 8 mg/kg.

Reference

1) Newman S L, Hanigan T P, Fisher A, et al.: Clinically Significant Mucosal Candidasis Resistant to Fluconazole Treatment in Patients with AIDS. Clin. Infect. Dis. 19: 684, 1994