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# Clinical Analysis of Treatment with Voriconazole for Invasive Fungal Infections of 69 Patients with Hematologic Diseases

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**The aim of this study was to investigate the efficacy and adverse effects of voriconazole in the treatment of invasive fungal infections (IFI) of the patients with blood diseases. The clinical manifestations and treatment of 69 cases of IFI patients with blood diseases were retrospectively analyzed. 39 cases were used voriconazole initially, 25 cases used voriconazole when fluconazol was inefficient. 5 cases used caspofungin and voriconazole together. In 69 patients with IFI, after treatment with voriconazole, 25 (36.23%) and 32 (46.38%) cases were clinically cured and obviously effective, respectively. The total effective rate was 82.60% (57/69). 6 (8.7%) and 6 (8.7%) cases were progressive and ineffective, respectively. During treatment, adverse reactions were found in 13 patients (18.84%, 13/69), including 3 cases with nausea, vomiting and increase of hepatic enzymes, 5 cases with rash, and 5 patients with visual disturbances and eye pain. Expectant treatment was treated on them, followed by continued use of voriconazole. The symptom was improved within 1 week. Voriconazole is an efficacious and well to le rated antifungal agent in the treatment of IFI in patients with hematologic disease.**

**Key words:** Voriconazole, Invasive fungal infection, Treatment, Hematologic disease.

In recent years, due to immune dysfunction in hematological malignancies, hormones, immunosuppressive agents, chemotherapy drugs and broad-spectrum antibiotics are used for long term, combined with central vein catheterization and bone marrow transplantation. So the occurrence rate of invasive fungal infection (IFI) increases year by year[1], especially for aspergillus and candida infection. IFI has become a very important complication and a key factor that affected long-term survival of patients with hematologic malignancies[2]. The clinical manifestation IFI is mostly atypical, with nonspecific imaging change. The fungal culture consumes long time, with a low positive rate. So it is difficult for early diagnosis of IFI. If IFI is not treated in time, the life of patient may be threatened[3,4]. In clinical research, the diagnosis of fungal diseases can be divided into suspected diagnosis, clinical diagnosis and confirmed diagnosis[1]. However, due to the low detection rate of fungal diseases, confirmed diagnoses of invasive fungal infections are relatively rare[3,4]. In most cases, empirical treatment is mainly used for suspected patients. In addition, the prognosis of patients with blood diseases complicated by invasive fungal infections is generally poor, especially the patients with agranulocytosis. Early diagnosis and early empiric treatment are particularly important for improvement of patients' prognoses[4-6].

Voriconazoleis a new kind of azole antifungals drug andhas a good antibacterial spectrum against aspergillus and candida. The action mechanism of voriconazole is that voriconazoleinhibitsdemethylation of 14±-sterol

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mediated by cytochrome P450 in fungus and thus inhibits biosynthesis ofergosterol[5]. The aim of this research is to evaluate the security and efficacy of empirical therapy with voriconazole for hematological malignancies complicated by invasive fungal infections.

## MATERIALS AND METHODS

### General information

69 cases of blood diseases were all patients of blood chemocherapy department hospitalized from May 2006 to May 2012. There were 48 males and 21 females, with the median age of 58 (17-89). In the 69 patients, there were 26 cases of acute myeloid leukemia (initial treatment, 19 cases; recurrence, 7 cases), 8 cases of acute lymphoblastic leukemia (initial treatment, 6 cases; recurrence, 2 cases), 17 cases of myelodysplastic syndrome, 12 cases of multiple myeloma and 6 cases of non-Hodgkin's lymphoma. Among them, 30 patients had been treated with fluconazole, caspofungin, itraconazole and other antifungal therapy, but those methods were ineffective. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The Second People's Hospital of Wenzhou. Written informed consent was obtained from all participants.

Invasive fungal infections mainly involved respiratory and digestive systems. The main manifestation was fever. Patients' body temperature ranged from 38.5 to 41.5!. Respiratory symptoms included dry cough, cough with expectoration, blood-stained sputum, chest tightnessand chest pain, heart palpitations and short breath etc. Those symptoms accounted for 82.9%(57/69). Hypoxemia and shock appeared in some severe cases. Digestive symptoms were nausea, anorexia, abdominal pain and diarrhea. They accounted for 13.0%(9/ 69). 3 patients of them involved two systems. Fungal septicemia accounted for 4.34%(3/69).

### Diagnostic criteria

On the basis of diagnostic criteria (7) of invasive fungal diseases (IFD) developed by European Organization for Research and Treatment of Cancer (EORTC) in 2008, cases were divided into 3 ranks: confirmed diagnosis cases, clinical diagnosis cases and suspected diagnosis cases, according to host factors, clinical criteria and microbiological criteria. Confirmed diagnosis cases: (1) with predisposing factors for fungal infections; (2) with clinical manifestations or imaging findings of fungal infections (main characteristics of lung imaging findings include aspergillus ball, nodules, voids, halo sign and crescent sign; secondary characteristics include other manifestations ofinflammation). (3) fungal infections were confirmed by sputum or nasal secretions culture or lung biopsy. Clinical diagnosis cases: (1) with predisposing factors for fungal infections; (2) with clinical manifestations or imaging findings of fungal infections. Suspected diagnosis cases: (1) with predisposing factors for fungal infections; (2) with clinical manifestations of infections. Persistent fever was treated with broad-spectrum antimicrobial drugs, but they were ineffective.

### The method of administration

Voriconazole injection was used for treatment. On the 1st day, the dose was 6mg /kg, once every 12 hours. From the 2nd day, the dose was kept at 4 mg /kg, once every 12 hours. When the treatment was effective or stable, 200mgvoriconazole tablets were given for oral sequential therapy twice a day. The injection duration was 3-35 days (average, 14 days), and sequential oral administration duration was 7-92 days (average, 20 days). The total treatment duration was about 31 days. Patients with impaired renal function or elderly patients were treated by oral voriconazole therapy. On the 1st day, the dose was 400 mg, once every 12 hours. From the 2nd day, the dose was kept at 200 mg, twice a day. After stabilization of body temperature and improvement of clinical symptoms, sequential oral administration was performed. When accepted the voriconazole therapy, patients were treated with experiential therapy associated with broad-spectrum antimicrobial drugs, on the basis of clinical manifestations, microbial culture and sensitivity result. Some patients accepted granulocyte colony stimulating factor and gamma globulin supportive therapy. During the treatment, patients' temperature, respiratory symptoms and conditions of sign improvement were observed every day. Microbiology culture was inspected in time. Chest CT andgalactomannan (GM) test were followed up weekly.

**Efficacy evaluation**

In line with the guiding principles of clinical study on antibacterial drugs issued in 1993 by the Ministry of Health, confirmed cases with etiological evidences were divided into cured, obviously effective, progressive and ineffective cases. (1) Cured cases: symptom, sign, laboratory test and pathogenic test returned to normal. (2) Obviously effective cases: patients' conditions improved obviously, but one of the above 4 items did not return to normal completely. (3) Progressive cases: patients' conditions improved after administration, but the efficacy was not significant. (4) Ineffective patients: patients' conditions did not improve or even were aggravated 72 hours after administration. Effective rate was calculated according to cured cases and obviously effective cases. Cases with clinical diagnosis and recommended diagnosis were divided into obviously effective, progressive and ineffective cases.

(1) Obviously effective cases: clinical symptoms disappeared or obviously improved. (2) Progressive cases: clinical symptoms improved, but the efficacy was not obvious. (3) Ineffective cases: clinical symptoms did not improve or were aggravated. Effective rate was calculated according to obviously effective cases. Mycological efficacy criteria: according to EORTCcriteria, efficacy was evaluated comprehensively on the respects of clinical manifestations related to IFI, imaging and etiology, that is: compared with baseline, all the above indicators returned to normal, and that meant being cured; IFI symptoms and signs improved or disappeared or more than 50% of lesion was absorbed according to imaging, and that meant being obviously effective; imaging did not improved or less than 50% of lesion was absorbed, and that meant being stable; conditions of patients with IFI were aggravated or patients died for that reason, and that meant being ineffective. Effective rate=(the number of cured cases+ the number of obviously effective cases)/ the number of total cases.

**Monitoring of adverse reaction**

During treatment, liver function, kidney function, electrolytes, bloodroutine examination, X-ray chest radiograph or CT and etc. of all patients were reviewed at least once a week, and it was recorded that whether there were visual disturbances, rash, nausea, vomiting, diarrhea and other adverse reactions, as well as the severity, duration, processing method for adverse reactions and efficacy. In addition, the doses of other drugs, which were metabolized via CYP3A enzyme and CYP2C enzyme and used in the same period, were adjusted.

**Statistical method**

SPSS 13.0 was used for data analysis. Enumeration data were expressed as percentage. Chi-square test was used. If $P < 0.05$, the difference was statistically significant.

## RESULTS

**General data**

In 69 patients, there were 11 cases with confirmed diagnosis. Among them funguses were found in blood culture of 9 patients (5 cases with candida albicans, 2 cases with candida tropicalis and 2 cases with aspergillus), and aspergillus hyphae were found in other 2 cases by histopathological examination with nasal incision and drainage. There were 43 cases with clinical diagnosis, including 18 cases with mycology basis (6 cases with aspergillus, 10 cases with candida, and 2 cases with saccharomycetes). Other 50 patients were examined by GM test (<0.5, 2 cases; >0.8, 39 cases; >1.0, 9 cases). In addition, 15 patients were with suspected diagnosis.

**Laboratory test**

Fungal infectionsof all 69 patients occurred in granulocytopenic phase. The granulocyte density of 50 patients (72.46%) was $0.5\times 10^9$/ L and the granulocyte density of 19 patients (27.53%) was more than $0.5 \times 10^9$/ L. There were 53 patients (76.81%) whose granulocytopenic phase lasted for more than 2 weeks.

**Imaging test**

60 patients (86.96%) had lung imaging abnormalities. 23 patients (38.33%) had manifestations of main characteristics, and 37 patients (61.67%) had manifestations of secondary characteristics. 2 patients (2.90%) had multiple low density image of right liver lobe in CT. 12 patients (17.39%) had no imaging abnormality.

**Application of antibiotics**

All 69 patients were complicated by fever. Median duration time of body temperature which was higher than 38.0 ! was 5 days. All patients

whose granulocyte density was lower than 2.0× $10^9$/ L were treated with granulocyte colony stimulating factor to stimulate the growth of leukocyte. 10 patients with hematologic malignancies in this group were not eased. 58 patients had bone marrow suppression after chemotherapy. The density of neutrophile granulocytes in peripheral blood of 43 patients was lower than 0.5× $10^9$ /L for more than 10 days. 2 patients used hormone for a long term. All patients had been treated with broad-spectrum antibacterial drugs (imipenem, meropenem, third-generation cephalosporins, glycopeptide antibiotics, fluoroquinolones and drugs for treatment of anaerobic infections etc.). 39 patients were treated with voriconazoleat conventional dose during initial treatment. 25 patients were changed to use voriconazole for the ineffective treatment with fluconazole. 5 patients used caspofungin combined with voriconazole.

**Microbiological test**

Candida albicanswas found inrepeated sputum smears of 20 patients. Aspergillus was found in sputum of 13 patients. Candida glabrata was found in sputum culture of 20 patients. Funguses (5 caseswith candida albicans, 2 cases with candida tropicalisand 2 cases with aspergillus) were found in blood culture of 9 patients. 50 patients were examined by GM test. 2 cases, <0.5; 39 cases, >0.8; 9 cases, >1.0.

**Clinical efficacy**

After the treatment with voriconazole, there were 25 (36.23%) clinically cured cases, 32 (46.38%) obviously effective cases, 6 (8.70%) progressive cases and 6 (8.70%) ineffective cases. The total effective rate was 82.60%. The median time of temperature recovery was 3.8 days (2-19 days). The temperature of 20 patients returned to normal 2 days after administration. In 15 cases with suspected diagnosis, including 10 (66.7%) cured cases and 5 (33.3%) obviously effective cases. In 43 cases with clinical diagnosis, there were 13 (30.2%) cured cases, 25 (58.1%) obviously effective cases, 4 (9.3%) progressive cases, and 1 (2.3%) ineffective case. In 11 cases with confirmed diagnosis, there were 2 (18.2%) cured cases, 2 (18.2%) obviously effective cases, 2 (18.2%) progressive cases, and 5 ineffective cases. There was no significant difference of total effective rate between suspected diagnosis group and clinical diagnosis group, but that in confirmed group was significantly lower than suspected diagnosis group and clinical diagnosis group, respectively ($P < 0.05$).

**Adverse reactions**

69 patients had blood neoplastic diseases and needed various treatments. Due to the complex medication and non-blood system underlying diseases of some patients, adverse reactionsoccurred during treatment, which could not be excluded from reactions related to voriconazole, were involved in statistical analysis. Adverse reactions were found in 13 (18.84%, 13/ 69) patients, including 3 cases with nausea, vomiting and increase of hepatic enzymes, 5 cases with rash, and 5 cases with visual disturbances and eye pain. Expectant treatment was treated on them, followed by continued use of voriconazole. The symptom was improved within 1 week.

## DISCUSSION

In recent years, the occurrence rate of invasive fungal infection of patients with hematological tumorshas significantly increased. Once IFI is not effectively controlled, it will become one of the common causes of death of these patients (2). It is reported that the occurrence rates of IFI of patients with acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome and lymphoma are 35.4%, 43.6%, 22.2% and 10.5% respectively (2). Common risk factors of fungal infection in include abnormal immune function, long-term use of hormones and immune inhibitors, high-dose chemotherapy, use of broad-spectrum antibiotics, central venous catheterization, bone marrow transplantation and granulocyte deficiency. In hematological malignancies such as acute myeloid leukemia, acute lymphoblastic leukemia, multiple myeloma and lymphoma, and myelodysplastic syndrome, the occurrence rate of IFI increases year by year, especially for aspergillus and candida infection (4-6).

In this study, patients treated with immunosuppressive agents, hormonal or chemotherapy drugs accounted for 70%-90% of total cases. All patients had fever symptoms (> 38 $^oC$, median time of 5 day), in which the respiratory and digestive system were involved. Respiratory

symptoms included cough, cough complicated with stethocatharsis, bloody sputum, chest tightness and chest pain, palpitation, and gas tightness, accounting for 81.2% (56/69), with hypoxemia and shock symptom in partial cases. Digestive system symptoms included nausea, anorexia, abdominal pain and diarrhea, accounting for 13% (9/69). In 3 cases both 2 systems were involved. 9 cases were with fungal septicemia, accounting for 13% (9/69). 62.3% of IFI patients were with clinical diagnosis, and 15.9% of IFI patients were with confirmed diagnosis. The clinical manifestations were not typical, even though there were one or more host factors. The halo sign and air crescent sign of which chest CT examination was valuable only occurred in 24 cases. Most imaging changes were non-specific shadows. Fungal culture consumes long time, with a low positive rate. So it is difficult for early diagnosis (8). Previous studies (7,9,10) find that, GM test result is a sensitive indicator for early diagnosis of IFI. Pazos et al. suggest that, GM test should be performed in early stage, thus the specificity of IFI can be increased to 100% (7).

The selection of antifungal drugs is complex and difficult according to clinical result. Security and efficacy of drugs must be considered as well as interaction between drugs and the cost of treatment. Currently, drugs for treatment of IFI mainly include triazoles, such as fluconazole and itraconazole, polyenes, such as amphotericin B, and echinocandins, such as caspofungin. Antibacterial spectrumof fluconazoleis relatively narrow andthe resistance rate of fungal is relatively high. Fluconazole has no antibacterial activity againstaspergillus and certain kinds of Candida. The antibacterial spectrum of itraconazole is broader than that of fluconazole, but resistant strains appeared too in recent years. Though the efficacy of amphotericin B is high, most patients cannot tolerate it due to its serious adverse reaction, which limits itsextensive use. Voriconazole is a kind of broad-spectrum antifungal triazole. The mechanism is that voriconazole inhibits demethylation of 14 - a- sterol mediated by cytochromeP450 and thus inhibits the biosynthesis ofergosterol for antifungal activity (7,8,11). It is found in voriconazole in vitro susceptibility test as follows: compared with fluconazole and itraconazole, voriconazole has obvious bacteriostasis against candida which has resistance against fluconazole and itraconazole, in addition to the antifungal activity againstcandida. Besides, it has good antibacterial activity against fluconazole-resistant serious invasive candidiasis (Candida krusei and Candida glabrata) (7,9,10). Voriconazole has broad antibacterial spectrum, and has strong antibacterial activities for yeast, candida (especially for candida krusei and candida glabrata), aspergillus and fusarium. Oral administration can obtain complete absorption, with high bioavailability (96%), wide tissue distribution, and high concentration in cerebrospinal fluid. In American Society for Infectious Diseases (IDSA), voriconazole is used in first-line therapy of aspergillus infection (7,10).

In this study, 69 patients with blood tumors complicated by IFI were treated with voriconazole. There were 25 (36.23%) clinically cured cases, 32 (46.38%) obviously effective cases, 6 (8.70%) progressive cases and 6 (8.70%) ineffective cases. The total effective rate was 82.60%. The median time of temperature recovery was 3.8 days (2-19 days). The temperature of 20 patients returned to normal 2 days after administration. The treatment efficacies in clinical diagnosis group and suspected diagnosis group were obviously better than confirmed diagnosis group. In 11 cases with confirmed diagnosis, there were 2 clinically cured cases, 2 obviously effective cases, 2 progressive cases, and 5 ineffective cases. This indicates that, when clinical infection symptom and positive result of fungal indirect test appear in blood disease patients, the treatment with voriconazole should be immediately performed, followed by antifungal therapy. A retrospective cohort study was conducted on the relation between antifungal therapy beginning time and mortality in 157 patients with candidemia from January 2001 to December 2004. Results showed that, when antifungal therapy was performed within 12 h after collecting sample for first positive blood culture, the mortality rate of patient was only 11.1%. If the time exceeded 12 h, the mortality rate was as high as 33.1%. This indicates that, early antifungal therapy is very important. The treatment course of voriconazole varies in different patients. In this study, the injection duration is 3-35 day (average, 14 day), and sequential oral administration duration is 7-92 day (average, 20 day). The total treatment duration is about 31 day.

Factors effecting efficacy include N absolute value, fungus genus, complication of bacterial infection, and GM test result. The mortality rate in patients with extreme N lack is significantly increased, suggesting that the treatment with G-CSF should be performed in antifungal therapy. The mortality rate due to aspergillus infection is significantly higher than candida infection. So more attentions should be paid to aspergillus infection. In addition, when patients are complicated with Gram-negative bacilli bloodstream infections, the mortality rate is obviously increased. So flexible adjustment of antibiotic and antifungal treatment time is necessary. After treatment, if the GM test result can not decrease to normal, the prognosis may be poor. Dynamic GM test can be used as an indicator for determining prognosis (7,9).

It was found by Denning et al. (8) that the efficacy of voriconazole for treatment of invasive aspergillus infection was higher than that of conventional amphotericin B; compared with itraconazole, voriconazole had pharmacoeconomic advantages. That is similar to the conclusion of this research. In this research, the total effective rate of 69 patients in voriconazole group was 82.60% (57/69), which suggested the high effective rate of voriconazole. 25 cases (36.23%) were clinically cured. The low cure rate may be related to malignant diseases, low immunity and agranulocytosis of most patients. The imaging changes were relatively slow, which also affected the evaluation of efficacy. Patients in this group included 13 cases with poor efficacy of fluconazole, 3 cases with poor efficacy of itraconazole and 1 case with poor efficacy of caspofungin. After the treatment of voriconazole, total effective rate was still 82.60% (57/69). That suggests that voriconazole has certain efficacy in treatment of IFI as both first-line drug and second-line drug. In addition, that suggests that voriconazole is a desirable choice for patients with no efficacy of other first-line drugs. That is similar to references (12-14). In this research, it was also shown that voriconazolehadrelatively high security. The incidence of adverse reactions was only 18.84% (13/69). The adverse reactions were mainly side reactions of level 1-2, such as liver dysfunction, rash, gastrointestinal reactions and visual impairment etc. Expectant treatment was conducted for above adverse reactions, followed by continued use of voriconazole. The symptom was improved within 1 week (15-17). That suggested that patients with blood tumor complicated by IFI had good tolerance on voriconazole (12,18,19).

In this research, it is initially suggested that voriconazole has good efficacy in treatment for IFI of patients with blood tumors, as both first-line drug and second-line drug. Meanwhile, its adverse reactions are less and most of them can be tolerated. Voriconazole is an effective and safe broad-spectrum antifungal drug. And it may become the preferred drug in the treatment for IFI of patients with blood tumors. Early use of voriconazole can improve the efficacy and reduce the mortality in fungal infections.

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