RESEARCH COMMUNICATION

Phase II Study on Voriconazole for Treatment of Chinese Patients with Malignant Hematological Disorders and Invasive Aspergillosis

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Abstract

Objective: To investigate the efficacy and safety of voriconazole in treating Chinese patients with hematological malignancies and invasive aspergillosis. Methods: From March 2007 to April 2012, patients with diagnoses confirmed by CT, GM test and/or PCR assays, were recruited into this study. Aspergillosis of all patients were treated with voriconazole 6 mg/kg intravenous infusion (iv) every 12 h for 1 day, followed by 4 mg/kg IV every 12 h for 10-15 days; Then, switch to oral administration that was 200mg every 12h for 4-12 weeks. Efficacy and safety were evaluated according to Practice Guideline of Infectious Diseases Society of America. Results: The overall response rate of 38 patients after voriconazole treatment was 81.6%. The median time to pyretolysis was 4.5 days. Treatment related side effects were mild and found in only 15.8% of cases. No treatment related deaths occurred. Conclusions: Voriconazole can considered to be a safe and effective front-line therapy to treat patients with hematological malignancies and invasive aspergillosis. Alternatively it could be used as a remedial treatment when other antifungal therapies are ineffective.

Keywords: Hematological disorders - aspergillus - voriconazole

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Introduction

In recent years, the incidence of invasive fungal disease is significantly increased in patients with malignant hematological disorders, with main risk factors including long-term or repeated cycles of chemotherapy, administration of broad-spectrum antibiotics and stem cell transplantation (Hoenigl et al., 2012). In high-risk patients, the mortality rate of aspergillosis disease is reported to reach as high as 80% (Nicolle et al., 2011). However, conventional treatment in this setting is unsatisfactory, eg., itraconazole is low in its bioavailability and further could induce drug resistance, amphotericin B is associated with severe adverse reactions (Miller et al., 2011). On this background, it is urgent to develop a medication to cope with invasive aspergillosis in patients with malignant hematological disorders.

Voriconazole is a second-generation synthetic triazole antifungal regimen, a derivative of fluconazole. The antibacterial spectrum of voriconazole is broad, with good antifungal activity by intravenous or oral administration. It is suggested that voriconazole could be considered as first line or salvage treatment for patients with invasive fungal disease (Metzke et al., 2012). To observe efficacy and safety of voriconazole in treating invasive aspergillosis for patients with malignant hematological disorders, we conducted current study.

Materials and Methods

Patient Eligibility

Patients were required to be pathologically/cytologically diagnosed with malignant hematological disorder from March 2007 to April 2012; to sign an informed consent before treatment; to expose to long term chemotherapy or supportive care; to have a score of karnofsky performance status ≥ 70, and to be followed until the end of this study. Other eligibility criteria included: adequate hematological (white blood cell count > 3.0×10^9 and platelet count > 150×10^9), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine leval < 1.5 times the upper normal limit); patients were excluded from the study if they had active cardiac disease (LVEF < 50%), significant arrhythmia, any serious medical or psychiatric condition.

Methods

Clinical diagnostic criteria: Definition of invasive fungal infection is in line with previous report (Nicolle et al., 2011). Clinical diagnosis could be confirmed if at least

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one Patient, one Primary or two Supplementary Clinical and one Experimental criteria were satisfied. Patient criteria, (1) reduction of neutrophil cells ($< 0.5 \times 10^9$/L) for more than 10 days (2) body temperature > 38 ºC or < 36 ºC, and have an record of neutrophils reduction (more than 10 days) in 60 days, or received an immunosuppressant in 30 days (3) medical history of fungal infections, or graft versus host disease, etc; Primary Clinical criteria, evidence of respiratory infection: halo, crescent-shaped air sign, or consolidation appeared vacuole on pulmonary CT scan; Supplementary Clinical criteria: (1) symptoms of lower respiratory tract infection: cough, chest pain, hemoptysis, breathing difficulty, etc. (2) evidence of nasal and sinus infections is mainly established through radiological evaluation with a suggestion of invasive infection of the sinuses parts, that could be accompanied by upper respiratory symptoms, nasal ulceration, nasal bleeding, periorbital swelling and maxillary sinus tenderness; Experimental criteria: Galactomannan (GM) or Aspergillus PCR tested positive more than 2 times in peripheral blood.

Treatment: Voriconazole 400 mg (Pfizer Inc., brand name in China: Weifan) is intravenously infused for 12 hours on the first day of diagnosis. From the second day, voriconazole 200mg, 12 hours intravenous will be continued for 10 to 15 days, then switched to 200 mg twice daily oral maintenance for a period of 4-12 weeks according to patient condition. During treatment, CT scan, serum GM test and/or aspergillus fluorescent PCR detection will be repeated every week, for a total of 3 ~ 5 weeks.

Efficacy evaluation: Clinical efficacy, based on improvement of symptom and signs of patient, is classified as: Complete response (CR), Partial response (PR), Improved, and Invalid. CR: the symptoms and signs completely disappeared, and radiographic performance completely disappeared. PR: most symptoms and signs improved and disappeared, at least 50% of radiographic performance improved. Improved: the signs and symptoms are moderately improved, but less than 50% of radiographic performance improved. Invalid: clinical symptoms and signs unchanged or deteriorated. Effective cases is the sum of CR and PR. For effective cases, GM test and Aspergillus fluorescence PCR turned negative; for invalid cases: these results remain positive.

Table 1. Pyretolysis Time and Clinical Efficacy of 38 Patients Treated with Voriconazole

	Acute leukemia n=24	Multiple myeloma n=8	Lymphoma n=6
Cycles of chemotherapy			
M±SD	4.8±2.8	5.6±2.4	5.0±0.6
Day of voriconazole therapy			
M±SD	52.8±13.9	55.1±13.7	61.0±15.9
Pyretolysis period (day)			
M±SD	4.8±2.0	4.8±2.1	4.8±1.3
Clinical efficacy of voriconazole			
Complete response n(%)	6(25.0)	2(25.0)	0(0.0)
Partial response n(%)	13(54.2)	5(62.5)	5(83.3)
Improved n(%)	3(12.5)	1(12.5)	0(0.0)
Invalid n(%)	2(8.3)	0(0.0)	1(16.7)

M±SD, mean±standard deviation; n(%), number (percentage)

Safety: During voriconazole treatment, all adverse reactions and abnormalities in laboratory tests are documented.

Statistical analysis: Continuous variables were summarized by descriptive statistics, categorical variables by frequency. Count data by Chi-square test; measurement data as mean ± standard deviation. $P < 0.05$ was considered statistically signifcant. The study data was analyzed through the STATA 8.0 software (Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845 USA).

Results

Patient characteristics

From March 2007 to April 2012, 38 patients with hematologic malignancies and invasive aspergillosis satisfied all study criteria. Among them, 22 were male and 16 female, average age was 56±14 years. All patients had completed medical records, including results of CT scan and serum galactomannan(GM) test and/or aspergillus fluorescence PCR assay. Of all 38 patients, 24 diagnosed with acute leukemia, 8 multiple myeloma, 6 malignant lymphoma. After received chemotherapy (12 patients had 1-3, 16 had 4-6 and 10 had more than 7 cycles), and experienced neutrophil decrease (6 cases were to $< 1.0 \times 10^9$/L, 24 cases to $< 0.5 \times 10^9$/L, 8 cases to $< 0.2 \times 10^9$/L), all patients experienced fever, with body temperature > 38 ºC. Two patients reported nose bleeding and nasal collapsing, 29 complained coughing and chest pain, 6 recorded hemoptysis with filamentous sputum, and one patient told chief physician with headache and vomiting. Regarding invasive aspergillosis, 2 cases were confirmed with nasal, 35 with pulmonary, and 1 with central nervous system infection.

CT scan: Nasal CT of 2 patients suggested invasive infection of sinus, and nasal septum deviation. Chest CT scan of 31 patients revealed halo, crescent-shaped air sign, or other signs of invasive fungal disease.

GM test and Aspergillus Fluorescent PCR Detection: Of all 38 patients checked by serum GM test and/or Aspergillus fluorescent PCR, 21 were serum GM test positive, and 38 were Aspergillus Fluorescent PCR Detection positive.

Clinical analysis

For 5 patients, with no improvement after 1 week itraconazole as front line treatment, the regimen was switched to voriconazole. The rest 33 patients were treated by voriconazole immediately after clinical diagnosis, and the average period of fever for these patients was 54.7±17.8 days, and voriconazole was maintained 12 weeks. Response rate after voriconazole treatment was 81.6% (Table 1). Fever clearance time: for 38 patients, 35 achieved fever (92.1%) clearance, average fever clearance time was 4.5 days (2 to 10 days) after treated by voriconazole.

GM test results: Among 21 patients with positive serum GM test, 6 (28.6%) negativity was confirmed after 1 week voriconazole treatment, 10 (47.6%) negativity after 2 weeks, 15 (71.4%) after 4 weeks, and 18 (85.7%) after voriconazole treatment.

Aspergillus fluorescence PCR results: Among 38 patients with Aspergillus Fluorescent PCR Detection positive, after 1 week voriconazole treatment, 5 (13.6%) turned negative; after 2 weeks, 12 (31.6%) negative; after 4 weeks, 20 (52.6%) negative; after voriconazole treatment was completed, 25 (65.8%) was negative.

Adverse reactions

Of 38 patients treated by voriconazole, 6 (15.8%) patients reported adverse reactions: 3 complained short visual obstacle, 2 experienced nausea and vomiting and 1 recorded skin rash. After treatment, all adverse reaction disappeared. No treatment realated death was documented.

Follow-up

By the end of May 2012, aspergillosis of 12 patients was effectively controlled, but these patients died of hematologic malignancies. Ten patients received voriconazole treatment for 4-6 weeks, but discontinued treatment because of financial difficulties, poor efficacy or other reasons, and eventually died of invasive aspergillosis. Two patients lost follow-up. Aspergillosis of rest 14 patients was well controlled. And these 14 patients are still alive and in the treatment of hematologic malignancies.

Discussion

Due to the aggressiveness of invasive aspergillosis, early diagnosis become extremely important (Kriengkauykiat et al., 2011; Baddley et al., 2012; Ohba et al., 2012). In clinic setting, CT combined with fiberoptic bronchoscopy, bronchoalveolar lavage and biopsy are commonly recommened diagnostic methods (Godet et al., 2012; Reinwald et al., 2012). However, limitations of biopsy make it applicable only to part of patients (Wang et al., 2012). In recent years, with a widespread application of serum GM and aspergillus fluorescent PCR tests, early diagnosis of aspergillosis is significantly improved (Springer et al., 2012; Tabarsi et al., 2012). GM test is a method which adopts serum enzyme-linked immunosorbent assay to detect aspergillus galacto-glucomannan antigens, to confirm a diagnosis of aspergillosis (Godet et al., 2012; Reinwald et al., 2012; Stopiglia et al., 2012; Tabarsi et al., 2012). The sensitivity of GM test was 50-90% and the specificity was 80-90%, and usually demonstrating positive before the emergence of radiological evidence (Horbrecht et al., 2002; Georgiadou et al., 2012). The sensitivity of aspergillus fluorescence PCR for diagnosing aspergillus infection is high, but should pay attention to false positive that could be caused by confounding factors, eg., laboratory pollution. However, aspergillus fluorescence PCR negative could rule out aspergillus infection (Mengoli et al., 2009; White et al., 2010).

Commonly recommended medications for aspergillosis include itraconazole, amphotericin B, caspofungin and voriconazole,etc, and the efficiency various in different reports (Wingard et al., 2011; Egerer et al., 2012; Hadrich et al., 2012; Yuan et al., 2012). Voriconazole is a second-generation synthetic triazole antifungal drug, a derivatives of fluconazole. The antimicrobial spectrum of voriconazole is broad, and has a good antifungal activity both through oral or intravenous administration, has synergistic effect with caspofungin (Sambatakou et al., 2006; Kim et al., 2011; Maschmeyer et al., 2011; Tashiro et al., 2012). Its efficacy in the aspergillosis treatment is better than amphotericin B, has become the first-choose drug (Herbrecht et al., 2002; Hilde et al. 2008; Misra et al., 2011; Schwartz et al., 2011). Voriconazole is supposed to pass through the blood-brain barrier, so mostly recommended for patients with central nervous system aspergillosis (Stefan et al., 2005; Schwartz et al., 2011).

This study focused on voriconazole in the treatment of a cohort of Chinese patients with invasive aspergillosis and hematologic malignancies, and was coducted in Nanjing, China. Some of information regarding research and clinical work of this area has been introduced in detail elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Gong et al., 2012; Yu et al., 2012). During this study, several points were noticed: First, for patients with chemotherapy accociated leucopenia, CT and GM tests should be carefully considered to confirm the diagnosis of invasive aspergillosis if fever is presented or conventional antibiotic is proved invalid; Second, among our patients with invasive aspergillosis, 3 were infected in the same room of hospital in a short period, reminds us that much attention should be paid to the invasive aspergillosis infection in hospital; Third, once diagnosis is established, antifungal therapy should be administrated promptly and voriconazole could be a priority.

In conclusion, in this study, the effective rate of voriconazole in treating patients with hematologic malignancies and invasive aspergillosis was 81.6%. Five patients had been treated by itraconazole for 1 week and was invalid, and switched to voriconazole therapy. Eighteen patients had GM test negative, 25 with Aspergillus PCR detection negative. Average fever clearance time was 4.5 days and found no serious adverse reactions. The association between GM test and Aspergillus PCR assay with the diagnosis of invasive aspergillosis needs to be further analyzed.

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