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Original Article

Efficacy and predictive factors of intravenous itraconazole empirical treatment for patients with hematological malignancies suspected of invasive fungal disease

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Abstract: To evaluate the efficacy and safety as well as the predictive factors for overall success of (intravenous) IV itraconazole empirical treatment for patients with hematological malignancy. Eighty-two possible or probable invasive fungal disease (IFD) patients with hematological malignancy were enrolled in this cohort study. Patients were treated with IV Itraconazole for empirical treatment. After completion of IV itraconazole, 42 (51.2%) patients achieved overall success. The numbers and rates of patients reached absence of breakthrough fungal infection, resolution of fever prior to recovery from neutropenia and survival for above 7 were 74 (90.2%), 58 (70.7%) and 82 (100%), respectively. Among all patients, 50 (61.0%) patients showed no premature discontinuation. Nausea and vomit was observed in 6 (7.3%) patients, and hypohepatia was found in 4 (4.9%) patients. While hyperpyrexia and shiver existed in only 2 (2.4%) patients. Univariate logistic regression was performed, and age (P = 0.002), ECOG performance status (P = 0.009) as well as duration of baseline fever (P = 0.008) were correlated with overall success. And the multivariate logistic regression was performed, the analysis showed that age (P = 0.028) and duration of baseline fever (P = 0.023) were the independent factors predicting the overall success. This study revealed that IV itraconazole empirical treatment is effective and safe for patients with hematological malignancies, and age as well as duration of baseline fever could be served as convincing independently predictive factors for overall success of IV itraconazole empirical treatment.

Keywords: Efficacy, prognostic factor, itroconazole, empirical treatment, invasive fungal disease

Introduction

Patients with hematological malignancies are high risk population concurrent with invasive fungal disease (IFD) for their immunocompromised state, especially during chemotherapy [1-3]. Due to the usual delay of IFD diagnosis, the mortality and morbidity caused by IFD in patients with hematological malignancies are increasing over years [4]. Thus the routine antifungal prophylaxis (AFP) has been given to patients for IFD prevention, however the extra cost and unnecessary use of antifungal agents caused drug resistance have resulted in the reconsideration of AFP [5, 6], such that the empirical antifungal treatment has come into consideration and application in patients with hematological malignancy suspected of IFD.

Empirical antifungal treatment is usually for patients with prolonged neutropenic fever more than 3-7 days with no response to the broad spectrum antibiotics [7]. Although deoxycholate amphotericin B (D-AMB) and liposomal amphotericin B (L-AMB) are effective for IFD treatment, they have not been widely recommended for empirical treatment for their stiff prices and toxicities [8]. Azoles, a class of mold active antifungal agents that suppress the fungi infection through inhibiting the cytochrome (CYP) P450, have been recommended for empirical treatment in patients with high risk of IFD [9-11]. Itraconazole is a type of triazole with less toxicity compared with amphotericin B, and the broad spectrum of itraconazole has made it a frequent alternative for amphotericin B. In addition, itraconazole is now available in

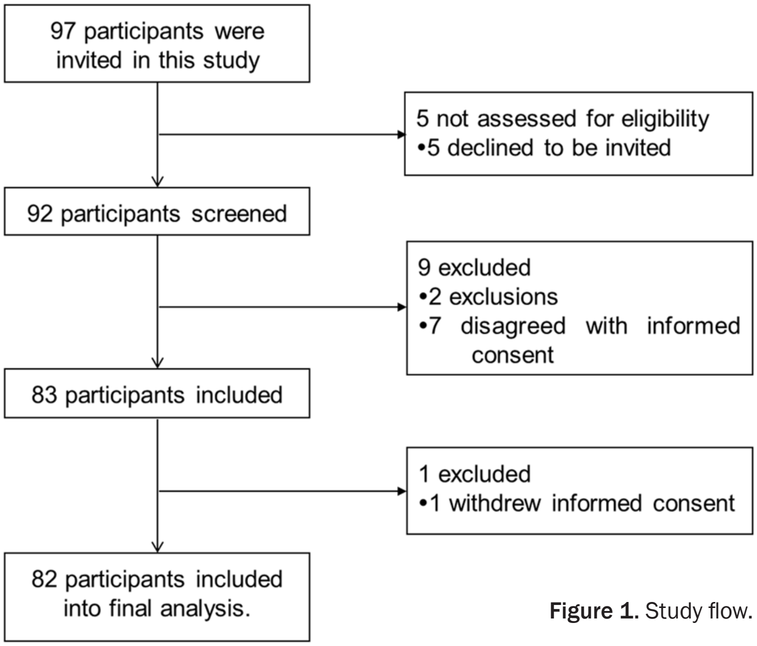

Figure 1. Study flow.

capsules, oral solution and IV injection, and the administration is relatively easy compared with other antifungal agents [12]. However, the efficacy of IV itraconazole empirical treatment and predictive factors for efficacy are not well investigated among patients with hematological malignancy over decades.

Therefore, we conducted a retrospective cohort study to evaluate the efficacy and safety as well as the predictive factors for overall success of IV itraconazole empirical treatment in patients with hematological malignancy.

Patients and methods

Participants

82 possible or probable IFD patients at Department of Hematology in Shanghai Tongji Hospital, from Jun. 2013 to Dec. 2015, were enrolled in this cohort study. The inclusion criteria were as follows: (1) Age above eighteen; (2) Possible or probable IFD according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria; (3) Malignant hematological diseases, diagnosed by morphology, immunology and cytogenetics; (4) Undergoing chemotherapy; (5) Persistent (more than 2 days) or recurrent neutropenic fever, despite empirical broad-spectrum systemic antibacterial therapy. In this study, fever was defined as a single oral temperature of above 38.3°C or a temperature of above 38.0°C twice within 24 hours, while neutropenia was defined as an absolute neutrophil count (ANC) < 500/μL, or an ANC < 1,000/μL with a predicted decrease to below 500/μL. The exclusion criteria were: (1) Documented (proven) IFD; (2) Complicated or history of solid cancers; (3) Severe liver and renal dysfunctions. Severe liver dysfunction was defined as an aminotransferase/alkaline phosphatase level above 5 times of the upper limit of normal (ULN), and severe renal dysfunction was defined as a calculated creatinine clearance < 30 mL/min; (4) Known allergy, intolerance or hypersensitivity to itraconazole; (5) Pregnancy or lactation.

This study was approved by the Ethics Committee of Shanghai Tongji Hospital, and all participants provided the informed consents.

Treatment

Intravenous (IV) Itraconazole (sipirennuo, Janssen Pharmaceutica, China) for empirical treatment was initiated at 200 mg every 12 hours at the first 2 days, and followed by 200 mg once a day after 2 days. For patients with no signs of treatment effectiveness or patients with disease progression, the IV itraconazole was discontinued and replaced by other antifungal agents. For patients with treatment effective, the IV itraconazole lasted up to more than 2 weeks.

Treatment efficacy and safety

The primary endpoint was overall success rate, which defined as achievement of the following items: Absence of any breakthrough fungal infection during itraconazole therapy and within 7 days after the completion of itraconazole treatment; Survival for above 7 days after completion of itraconazole; No premature discontinuation due to itraconazole related toxicity or lack of efficacy; Resolution of fever in setting of

Table 1. Baseline characteristics of patients treated by itraconazole

Parameters	Total patients (n = 82)
Age (range) (years)	42.5 (22-78)
Gender	
Male	42 (51.2%)
Female	40 (48.8%)
Underlying disease	
ALL	12 (14.6%)
AML	52 (63.4%)
NHL	6 (7.3%)
MM	12 (14.7%)
Disease status of underlying disease	
De novo	46 (56.1%)
Relapsed or refractory	36 (43.9%)
Previous HSCT	
Yes	13 (15.9%)
No	69 (84.1%)
ECOG performance status	
0/1	47 (57.3%)
2/3/4	35 (42.7%)
Duration of baseline fever	
< 5 days	24 (29.3%)
≥ 5 days	58 (70.7%)
Duration of baseline neutropenia	
< 7 days	26 (31.7%)
≥ 7 days	56 (68.3%)
Previous or concomitant treatments	
Antifungal prophylaxis	52 (63.4%)
Immunosuppressive agent	18 (21.9%)
Long-term use of steroid	12 (14.6%)
Complications	
Hypertension	39 (47.6%)
Diabetes mellitus	10 (12.2%)
Hyperuricemia	18 (22.0%)
Cardiac vascular disease	14 (17.1%)
Cerebrovascular disease	5 (6.1%)

Data was presented as median (range) or count (%). ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group.

neutropenia prior to recovery from neutropenia.

Safety profile was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Effects. And blood routine, liver and renal function, electrolytes, thoracic computerized tomography (CT) image were performed in patients and documented weekly; in the meantime, the adverse effects including the severity and duration of adverse effects as well as clinical characteristics were recorded.

Analysis of predictor for efficacy of itraconazole

Patients were divided into overall success group (OS group) and non-overall success group (NOS group) according to achievement of the overall success. And baseline factors were analyzed for predicting the achievement overall success to optimize the empirical use of itraconazole.

Statistics

Statistical analysis was performed using the SPSS 21.0 program in this study. Data was mainly presented as median and (range), count and (percentage). The influence of each factor at baseline on achievement of overall success was measured by univariate logistic regression, while all factors with a *P* value < 0.1 were further analyzed by multivariate logistic regression. A *P* value < 0.05 was considered significant.

Results

Baseline characteristics

Seventy-nine patients with hematological malignancy who had persistent or recurrent neutropenic fever were invited in this study, among them 5 patients were not assessed for eligibility (5 declined to be invited). Afterwards, the remaining 92 patients were screened for eligibility, and 9 patients were excluded after screening (2 exclusions and 7 disagreed with informed consent). Then 83 patients were included with 1 patient excluded for withdrew the informed consent. Finally a total of 82 participants were included into final analysis (**Figure 1**).

As presented in **Table 1**, the mean age of 82 patients is 42.5 (22-78) years, and 42 (51.2%) were male patients while 40 (48.8%) were female patients. Prior to the IV itraconazole empirical treatment, 52 (63.4%) patients were treated with antifungal prophylaxis, 18 (21.9%) patients were treated with immunosuppressive agent and 12 (14.6%) patients were long-term

Table 2. Overall success rate by itraconazole empiric treatment

Parameters	Total patients (n = 82)
Overall success rate (n, %)	42 (51.2%)
Absence of breakthrough fungal infection (n, %)	74 (90.2%)
Survival for above 7 days after completion of itraconazole (n, %)	82 (100%)
Resolution of fever prior to recovery from neutropenia (n, %)	58 (70.7%)
No premature discontinuation[a] (n, %)	50 (61.0%)

Data was presented as count (%). [a]No premature discontinuation due to itraconazole related toxicity or lack of efficacy.

Table 3. Safety profile of itraconazole empiric treatment

Parameters	Total patients (n = 82)
Nausea and vomit	6 (7.3%)
Hypohepatia	4 (4.9%)
Hyperpyrexia and shiver	2 (2.4%)

Data was presented as count (%).

steroid used patients. And the underlying diseases of patients were as follows: 12 (14.6%) acute lymphoblastic leukemia (ALL), 52 (63.4%) acute myelogenous leukemia (AML), 6 (7.3%) non-Hodgkin's lymphoma (NHL) and 12 (14.7%) multiple myeloma (MM). Among 82 patients, there are 46 (56.1%) *de novo* patients and 36 relapsed or refractory patients. And the duration of baseline fever was < 5 days in 24 (29.3%) patients and ≥ 7 days in 58 (70.7%) patients. The duration of baseline neutropenia was < 7 days in 26 (31.7%) patients and ≥ 7 days in 56 (68.3%) patients. Other baseline characteristics of patients were listed in **Table 1**.

Efficacy of itraconazole empirical treatment

After completion of IV itraconazole empirical treatment, 42 (51.2%) patients achieved overall success. In all patients, there were 74 (90.2%) patients achieved absence of breakthrough fungal infection, 58 (70.7%) patients achieved resolution of fever prior to recovery from neutropenia and 50 (61.0%) patients showed no premature discontinuation due to itraconazole related toxicity or lack of efficacy. And all 82 (100%) patients reached survival for above 7 days after completion of itraconazole (**Table 2**).

Safety of itraconazole empirical treatment

Adverse effects of IV itraconazole empirical treatment were documented, nausea and vomit was observed in 6 (7.3%) patients, and hypohepatia was found in 4 (4.9%) patients. While hyperpyrexia and shiver existed in only 2 (2.4%) patients (**Table 3**). IV itraconazole empirical treatment was withdrawn in 4 patients with hypohepatia as well as 2 patients with hyperpyrexia and shiver, and those adverse effects of the 6 patients were relieved after discontinuation of IV itraconazole empirical treatment. These indicated IV itraconazole empirical treatment were well tolerated in hematological malignancies.

Analysis of baseline factors for overall success

In order to explore the predict factors of overall success rate by itraconazole empirical treatment, univariate logistic regression was performed, and age (≥ 42.5 *vs.* < 42.5, OR = 0.241, 95% CI = 0.096-0.605; P = 0.002), ECOG performance status (0/1 *vs.* 2/3/4, OR = 3.382, 95% CI = 1.352-8.463; P = 0.009) and duration of baseline fever (< 5 days *vs.* ≥ 5 days, OR = 4.250, 95% CI = 1.470-12.285; P = 0.008) were manifested to be correlated with overall success rate by itraconazole empirical treatment. And the multivariate logistic regression was performed to analyze the factors with *P* value < 0.1 in univariate regression, the analysis discovered that age (≥ 42.5 *vs.* < 42.5, OR = 0.310, 95% CI = 0.108-0.883, P = 0.028) and duration of baseline fever (< 5 days *vs.* ≥ 5 days, OR = 3.913, 95% CI = 1.209-12.661, P = 0.023) were the independent factors predicting the overall success by itraconazole empirical treatment (**Table 4**).

Discussion

The results of our study illustrated that the overall success rate by IV itraconazole empirical treatment is 51.2% with 42 possible or probable IFD patients reached overall success, in the meantime the adverse effects of itraconazole in our study was relatively low. Finally, elderly patient was associated with poor overall success, while longer duration of baseline fever was a predictive factor of better overall success.

Table 4. Univariate and multivariate logistic regression analysis of the baseline factors for overall success by itraconazole empiric treatment

	Univariate logistic				Multivariate logistic			
	P value	OR	95% CI		*P* value	OR	95% CI	
			Lower	Higher			Lower	Higher
Age (years) (≥ 42.5 vs. < 42.5)	0.002*	0.241	0.096	0.605	0.028#	0.310	0.108	0.883
Gender (Male vs. Female)	0.504	0.744	0.312	1.773	-	-	-	-
ALL (Yes vs. No)	0.476	0.637	0.184	2.201	-	-	-	-
AML (Yes vs. No)	0.454	0.708	0.287	1.749	-	-	-	-
NHL (Yes vs. No)	0.434	2.000	0.345	11.578	-	-	-	-
MM (Yes vs. No)	0.254	2.118	0.584	7.681	-	-	-	-
Disease status (underlying disease) (De novo vs. R/R)	0.256	0.600	0.249	1.448	-	-	-	-
Previous HSCT (Yes vs. No)	0.420	1.647	0.490	5.540	-	-	-	-
ECOG performance status (0/1 vs. 2/3/4)	0.009*	3.382	1.352	8.463	0.280	1.789	0.622	5.145
Duration of baseline fever (< 5 days vs. ≥ 5 days)	0.008*	4.250	1.470	12.285	0.023#	3.913	1.209	12.661
Duration of baseline neutropenia (< 7 days vs. ≥ 7 days)	0.205	1.846	0.715	4.767	-	-	-	-
Antifungal prophylaxis (Yes vs. No)	0.098	0.459	0.183	1.155	0.234	0.519	0.176	1.529
Immunosuppressive agent (Yes vs. No)	0.345	1.673	0.576	4.862	-	-	-	-
Long-term use of steroid (Yes vs. No)	0.595	1.400	0.405	4.836	-	-	-	-
Hypertension (Yes vs. No)	0.190	0.556	0.232	1.336	-	-	-	-
Diabetes mellitus (Yes vs. No)	0.452	0.596	0.155	2.294	-	-	-	-
Hyperuricemia (Yes vs. No)	0.516	0.706	0.247	2.020	-	-	-	-
Cardiac vascular disease (Yes vs. No)	0.072	0.316	0.090	1.107	0.221	0.419	0.104	1.687
Cerebrovascular disease (Yes vs. No)	0.607	0.617	0.098	3.899	-	-	-	-

*P < 0.1, #P < 0.05. Data was presented as *P* value, OR (odds ratio) and 95% CI. A *P* Value < 0.05 was considered statistically significant. Significance was determined by univariate logistic regression analysis and all factors with a P < 0.1 were further analyzed by multivariate logistic regression. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group.

The impairment of immunes system caused by cytotoxic treatment, radiation therapy and leukaemic cell invasion in patients with hematological malignancies has made them at high risk of contracting IFD [3]. However, the timing and antifungal agent choices have always been issues of great debate among physicians for the toxicity and extra cost of certain antifungal agents. Itraconazole has been well established on its exposure-response reaction in animal models, despite its drug-drug interactions, its efficacy for IFD treatment in hematology patients was proved to be at least as equivalent as amphotericin B and other mold active azoles [13-19].

Our study identified an overall success rate of 51.2% by IV itraconazole empirical treatment, while trials evaluated the efficacy of empirical treatment of itraconazole in patients with hematological malignancies characterized overall success rates range from 56.5% to 70.4%, the results were higher than ours [14, 15]. However, a similar overall success rate, compared with ours, of 50% was reported by a single arm, prospective, multicenter study in Japan, which has a sample size of 86 patients [16]. The variation of success rates among former trials might due to the trials with higher overall success rates are larger sample size and multicenter trials [14, 15]. Furthermore, the criteria for overall success rate definition varied between studies, our study defined the overall success as achieved absence of breakthrough fungal infection, survival for above 7 days after completion of itraconazole, resolution of fever prior to recovery from neutropenia and no premature discontinuation, while some other study used the definition of response/(response + failure) or only assessed the response rate, which is defined as the number of responders divided by the total number of patients (those who responded, those who had treatment failure, and nonevaluable patients) [13, 15]. The prophylaxis use of itraconazole in patients with hematological malignancy is also evaluated by several studies, among them a success rate of 33.2% was reported [17-21].

In our study, the rate of nausea and vomit, hypohepatia, hyperpyrexia and shiver were little but not eliminated in patients. Itraconazole is illustrated to be of improved safety in patients with hematological malignancies against D-AMB and L-AMB, showing equal or relatively low incidence of infusion-related or metabolic-related adverse effects, the result is consistent with ours, which suggests itraconazole is well tolerated [18-21].

Our study disclosed that age and duration of baseline fever were identified as independently predictive factors of overall success in IV itraconazole empirical treatment for patients with probable or possible IFD. A multicenter, prospective observational study also illuminated age as a prognostic factor for the outcome of IV itraconazole empirical treatment in patients with hematological malignancies [22]. Poor ECOG performance status has also been identified in the same study, while it is not an independent factor in our study [22]. The duration of baseline fever ≥ 5 days was a predictive factor of poor overall success by IV itraconazole empirical treatment in our study, it might due to the fever is partly caused by neutropenia, and neutropenia is considered as the prominent risk factor for IFD [7].

Several limitations existed in this study: (1) some pharmaceutical treatments were not recorded in this study, which might resulted in somewhat bias in the results, and it is resulted from that itraconazole has some interactions with other drugs, such as coadministration of itraconazole and H2-receptor antagonists reduces their bioactivity [23]; (2) we did not assess the concentration of itraconazole in blood and it might be correlated with the overall success rate; (3) our study is a single arm retrospective cohort study with no controls included, which resulted in the overall success rate could not be compared. Nevertheless, the IFD in patients with hematological malignancies under chemotherapy is fatal, leading to the difficulty of conducting a randomized controlled trial.

In conclusion, this study revealed that IV itraconazole empirical treatment is effective and safe for patients with hematological malignancies, and age as well as duration of baseline fever could be served as convincing independently predictive factors for the overall success of IV itraconazole empirical treatment.

Disclosure of conflict of interest

None.

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