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Original Article

To what degree could clinical trials in evidence based medicine reflect reality in the treatment of candidemia?

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KEYWORDS
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Abstract *Introduction:* Evidenced based medicine (EBM) is necessary to standardize or treatment for infection since EBM is established based on the results of clinical trials. Entry criteria for clinical trials are very strict, and many patients have difficulties in being enrolled in any clinical trials regarding candidemia. It is questionable if the results of clinical trials reflect the real world of general medicine in this case.
Patients and methods: For the purpose of examining how many patients could join any randomized clinical trials for the treatment of candidemia, we reviewed all the candidemia patients in our institute during 2014—2018. The patients were divided into two groups: patients who were eligible for clinical trials (participation possible group), and those who were not (participation impossible group). Exclusion criteria for clinical trials were set based on previous clinical trials.
Results: A total of 70 patients was enrolled in this study. The median age was 73 years (range 36—93 years). Of these, 41 patients (59%) were male. As for site of infections, catheter related blood stream infection was most frequently seen in 37 (53%). Seventeen patients (24%) were classified as participation possible group and 53 patients (76%) were participation impossible group. Comparing the two groups, participation possible group patients have much better performance status, have less comorbidities and have longer overall survival times than participation impossible group patients.
Conclusion: Only 24% of candidemia patients were eligible for the clinical trials. Thus, we can see that clinical trials might not correctly reflect the real world among candidemia patients.

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Introduction

Evidenced based medicine (EBM) is established according to the results of clinical trials. Because of this, clinical trials are considered to be one of the most important undertakings and put at the top of priority among physicians in constructing therapeutic strategies. There is no room for doubt that current medicine is based on EBM. However, we skeptically think about that when we consider to what degree of candidemia patients were eligible for EBM.

Candidemia has emerged as an important nosocomial infection, with a 30–50% mortality rate.[1–3] It is the fourth most common nosocomial bloodstream infection (BSI) in the United States, and the seventh in Europe and Japan.[4–6] Candidemia patients have commonly one or more risk factors for candidemia like malignancy, diabetes mellitus, history of prior admission or surgical operation or history of surgery requiring the postoperative management in the ICU.[7–9] Some candidemia patients with cancer have received chemotherapy with or without palliative therapy. Despite these facts, entry criteria for clinical trials of candidemia set an exclusion criterion as follows; terminated cancer, receiving palliative therapy, having underlying diseases which are difficult to evaluate for therapy, or poor prognosis in that they are expected not to survive until the trial closes. Entry criteria for any clinical trial are generally strict, and most patients might not be suitable for the studies. Thus, it is reasonable to doubt if the results of clinical trials reflect the real world in general practice. This is the first report demonstrating that EBM could reflect to what degree candidemia patients in the real world are treated.

Patients and methods

Our institute is a 900-bed tertiary care center and is located in the countryside at Aichi prefecture in central Japan. For the purpose of examining how many patients in our institute could join any randomized clinical trials for the treatment of candidemia, we reviewed all candidemia patients in our hospital between September 2014 and May 2018. Candidemia was defined as at least with one positive blood culture of Candida species in patients hospitalized for more than 48 h with clinical signs and symptoms of infection. The patients were divided into two groups: patients who were eligible for clinical trials (participation possible group), and those who were not (participation impossible group). This study was approved by the Institutional Review Board of Aichi Medical University Hospital (16-H105).

Exclusion criteria commonly used in the many past ordinary clinical trials are as follows;[10–14]

1) Age < 16 years
2) Coexisting comorbidities or medical conditions which are difficult to evaluate for candidemia such as severe liver dysfunction, severe renal dysfunction (Severe liver dysfunction was defined as serum total bilirubin > the upper limit of the normal reference range × 3, or aspartate aminotransferase/alanine aminotransferase > the upper limit of the normal reference range × 5. Severe renal dysfunction was defined as serum creatinine > the upper limit of the normal reference range × 3)
3) Receiving immunosuppressive therapy
4) Coexisting fungal infective endocarditis, spondylitis or meningitis
5) Terminal stage hematologic or solid malignancies
6) Receiving chemotherapy for malignancy
7) Receiving palliative therapy due to any cause
8) Receiving prophylactic administration of any azole for more than 1 week within one month
9) Pregnancy
10) Poor prognosis (anticipated life expectancy < 30 days or patients who are not expected to survive until the end of the trial)

Patients' characteristics (age, sex), the Eastern Cooperative Oncology Group (ECOG) performance status (PS)[15] and Karnofsky Performance Status (KPS),[16] site of infections, pathogens isolated, outcome such as treatment, 30-day, or in-hospital mortality, coexisting disease and overall survival (OS) were evaluated. General conditions were evaluated by using ECOG-PS and KPS. Comorbidity was evaluated by the Charlson comorbidity index (CCI).[17] Overall survival time (OS) was calculated as from the date of diagnosis until the date of death from any cause. Disseminated intravascular coagulation (DIC) was diagnosed according to the diagnostic criteria developed by the Japanese Association for Acute Medicine (JAAM DIC diagnostic criteria).[6]

Performance status

General conditions were evaluated by using ECOG-PS[15] (PS 0: fully active. PS 1: restricted in physically strenuous activity but able to carry out work of a light nature. PS 2: up and about more than 50% of waking hours. PS 3: confined to bed or chair more than 50% of waking hours. PS 4: completely disabled, PS 5: dead) and KPS (KPS 100: normal or no complaints, 60: requires occasional assistance, but able to care for most of his needs, 20: very sick, 0: dead).

Identification of candida spp. and susceptibility testing

Candida species were identified by the VITEK-MS system (BioMerieux, Tokyo, Japan). Susceptibility to amphotericin B, caspofungin, fluconazole, itraconazole, and voriconazole was detected using the AST-YS07 card of VITEK-2 (BioMerieux, Tokyo, Japan). MIC values were interpreted according to species-specific clinical breakpoints as established by the Clinical and Laboratory Standards Institute (CLSI) for caspofungin (CPFG), fluconazole (FLCZ),

Table 1 Comparison of the two groups, clinical trial participation possible or impossible groups.

Variables	All patients (n = 70)	Participation possible group (n = 17)	Participation impossible group (n = 53)	*p*-value[a]
Age (mean years ± SD)	73 ± 12.1	74.1 ± 12.2	71.8 ± 12.1	0.503
Male sex (n, %)	41 (59)	14 (82)	27 (51)	0.015[a]
General conditions (mean points ± SD)				
ECOG- Performance Status	3.3 ± 0.8	2.8 ± 1.0	3.5 ± 0.7	0.023
Karnofsky Performance Status	42.6 ± 17.1	51.7 ± 14.7	39.6 ± 16.9	0.008
Site of infection (%)				
CRBSI	37 (53)	10 (59)	27 (51)	
Others	3 (4)	1 (6)	2 (4)	0.091[b]
Unknown	30 (43)	6 (35)	24 (45)	
Comorbidity (n, %)				
Cerebrovascular diseases	13 (19)	3 (18)	10 (19)	1.000
Heart diseases	24 (34)	4 (24)	20 (38)	0.347
Chronic pulmonary diseases	6 (9)	1 (6)	5 (9)	0.649
Diabetes mellitus	19 (27)	4 (24)	15 (28)	0.7
Liver dysfunction/disease	5 (7)	0	5 (9)	0.189
Malignancy	38 (54)	4 (24)	34 (64)	0.003
Renal disease/failure	13 (19)	0	13 (25)	0.024
Hemodialysis	6 (9)	0	6 (11)	0.147
Gastroesophageal reflux disease	3 (4)	1 (6)	2 (4)	0.709
Collargen diseases	6 (9)	2 (12)	4 (8)	0.589
Charlson Comorbidity Index (mean ± SD)	3.5 ± 2.7	1.2 ± 1.0	4.3 ± 2.6	<0.001
Severity (mean points ± SD)				
APACHE II score	12.9 ± 4.7	10.4 ± 3.6	13.7 ± 4.7	0.005
SOFA score	3.9 ± 3.2	2.8 ± 2.7	4.2 ± 3.3	0.096
SIRS score	1.9 ± 1.2	1.1 ± 0.	2.1 ± 1.2	0.001
Quick SOFA score ≧2 (n, %)	25 (36)	2 (12)	23 (42)	0.085[b]
Disseminated Intravascular Coagulation	9 (13)	2 (12)	7 (13)	1.000
Outcome Prognosis (n, %)				
30-day mortality	25 (36)	2 (12)	23 (43)	0.018[b]
In-hospital mortality	33 (47)	2 (12)	31 (58)	0.001[b]
Median overall survival time (month)	2.0	16.4	1.4	<0.001[c]
Initial anti-fungal treatment (n, %)				
Echinocandin	40 (57)	14 (82)	26 (49)	0.023
Liposomal amphotericin B	17 (24)	2 (12)	15 (28)	0.209
External device				
CVC/CV port	53 (76)	12 (71)	41 (77)	0.746[b]
Removal of devices within 24 h	29/53 (55)	6/12 (50)	23/41 (56)	0.751[b]
Reason of clinical trial participation not available (n, %)				NE
1) <16 years old	0		0	
2) Unassessed underlying diseases or medical conditions	33		33 (62)	

(*continued on next page*)

Table 1 (*continued*)

Variables	All patients (n = 70)	Participation possible group (n = 17)	Participation impossible group (n = 53)	*p*-value[a]
3) Immunosuppressive agents users	8		8 (15)	
4) Coexisting fungal endocarditis, spondylitis or meningitis	1		1 (2)	
5) Terminated malignancy	17		17 (32)	
6) Under chemotherapy	8		8 (15)	
7) Under palliative medicine	1		1 (2)	
8) Prophylactic administration	0		0	
9) Pregnancy	0		0	
10) Very poorer prognosis	21		21 (40)	
Candida spp. isolated (n, %)				
Candida albicans	27 (39)	3 (18)	24 (45)	0.049[b]
Non-*C. albicans*	43 (61)	14 (82)	29 (55)	

[a] *p*-value was evaluated comparing participation possible group and participation impossible group.
[b] Analyses were evaluated by Fisher's exact test.
[c] Analysis was used by Log–Rank test. Other factors were evaluated by student-t test.
APACHE II score, Acute physiology and chronic health evaluation II; CRBSI, catheter related blood stream infection; CVC, central venous catheter; CV port, central venous port; DIC, disseminated intravascular coagulation; ECOG, eastern cooperative Oncology group; SIRS, systemic inflammatory response syndrome; SD, standard deviation; SOFA score, sequential organ failure assessment score.

itraconazole (ITCZ) (only for *Candida albicans*), and voriconazole (VRCZ).[18] Susceptibility to amphotericin B (AMB) and Liposomal Amphotericin B (L-AMB) were interpreted according to species-specific clinical breakpoints as established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[19]

Statistical analyses

The data for categorical variables are expressed as percentages and continuous variables as mean ± SD or median with inter-quartile range (IQR). Chi-square or Fisher's exact test (two-tailed) was used to compare categorical variables and unpaired Student's t test or Mann–Whitney U test to compare continuous variables. Logistic regression analysis was used to identify independent risk factors associated with 30-day or in-hospital mortality of patients with candidemia. Statistical analyses involved use of SPSS version 26 for Windows (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Results

Seventy patients were enrolled in this study (Table 1). The median age was 73 years (range 36–93 years). Of these, 41 patients (59%) were male. As for site of infections, catheter related blood stream infection (CRBSI) was the most frequently seen in 37 (53%). The most common underlying diseases were malignancy in 38 (54%), followed by heart disease in 24 (34%). Mean CCI was 3.5. Median OS was 2 months. The 30-day and in-hospital mortality rates were 36% and 47%, respectively. Fifty-three (76%) had external devices such as central venous (CV) catheter or CV port. Seventeen patients (24%) were classified as participation possible group and 53 patients (76%) were participation impossible group. As for the reasons for clinical trial participation not available, unassessed underlying diseases or medical conditions were most commonly seen in 33 (62%), followed by having terminal malignancy in 17 (32%).

As for the candida species isolated, *C. albicans* was the most common among the *Candida* species identified, accounting for 39% of the cases, followed by *C. parapsilosis* (28%), *C. glabrata* (20%), *C. tropicalis* (10%) and others (9%). The most frequently used initial antifungal treatments were echinocandin (63%), and L-AMB (26%). All candida isolates were susceptible to initial antifungal agents based on CLSI and EUCAST breakpoints.

Comparing the two groups, participation possible group patients have much better PSs, have less comorbidities and have longer OSs (16.4 v.s. 1.4 months, p-value<0.001, by *Log-Rank* test) than participation impossible group patients as shown in Fig. 1. As for the severity of candidemia, participation possible group patients showed higher scores than participation impossible group patients (Table 1).

As for the correlation between the initial treatment and the prognosis in all patients, comparing echinocandin and non-echinocandin group, patients treated by echinocandins as initial agents showed a longer OSs than those treated by non-echinocandins (3 v.s. 1.4 months, p-value = 0.021, by *Log-Rank* test) (Fig. 2).

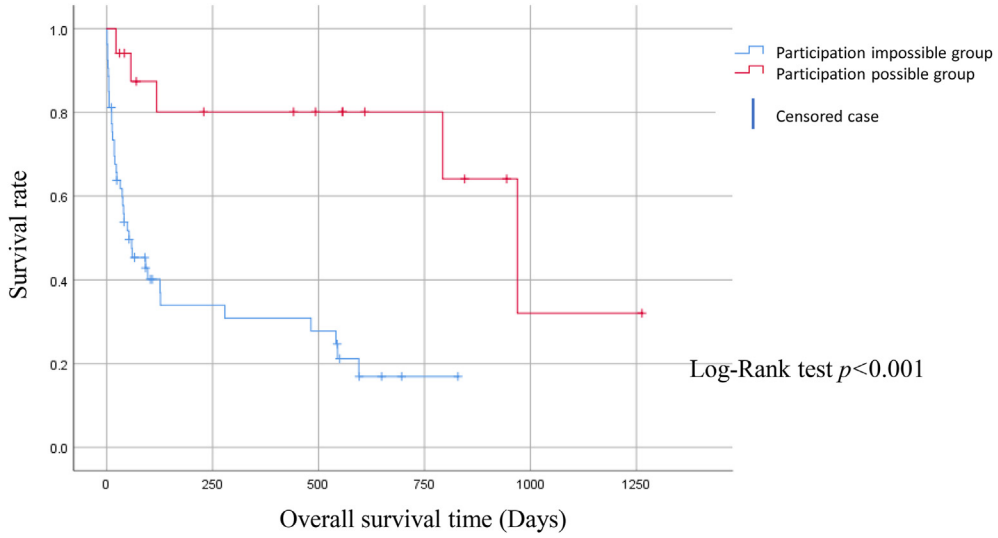

Figure 1. Shows overall survival according to participation possible (red line) and participation impossible group (blue line).

Comparing the 4 groups (group 1: echinocandins used in participation possible group, 2: other agents used in participation possible group, 3: echinocandins used in participation impossible group or 4: other agents used in participation impossible group) of OSs, there were no differences in group 1 and 2 (17.5 v.s.3.9 months, $p = 0.677$ by Log—Rank test) and 3 and 4 (2.1 v.s. 0.8 months, $p = 0.183$) (Fig. 3).

Discussion

EBM based on RCT is very limited in scope and EBM never reflected the real world as our result showed. Nevertheless, these days, some physicians tend to extremely rely on EBM, believe that RCT is the highest evidence for medicine and tend to be overconfident in EBM. They might not know the true nature of EBM. As some physicians may find, entry criteria for clinical trials for candidemia are very strict for patients with candidemia. Most candidemia patients have one or more risk factors for candidemia such as diabetes mellitus, malignancy with terminal stages, having external devices, receiving chemotherapy and/or palliative medicine and prior admission to ICU. General conditions of candidemia patients are commonly very severe and their life-expectancies are not long. In real world medicine, patients with these factors surely could be suspected as having candidemia. These patients should not be excluded from candidemia trials, even though some criteria are necessary for an appropriate evaluation.

Outstandingly, we found only 24% of the patients were eligible for clinical trials of candidemia. Previous report by

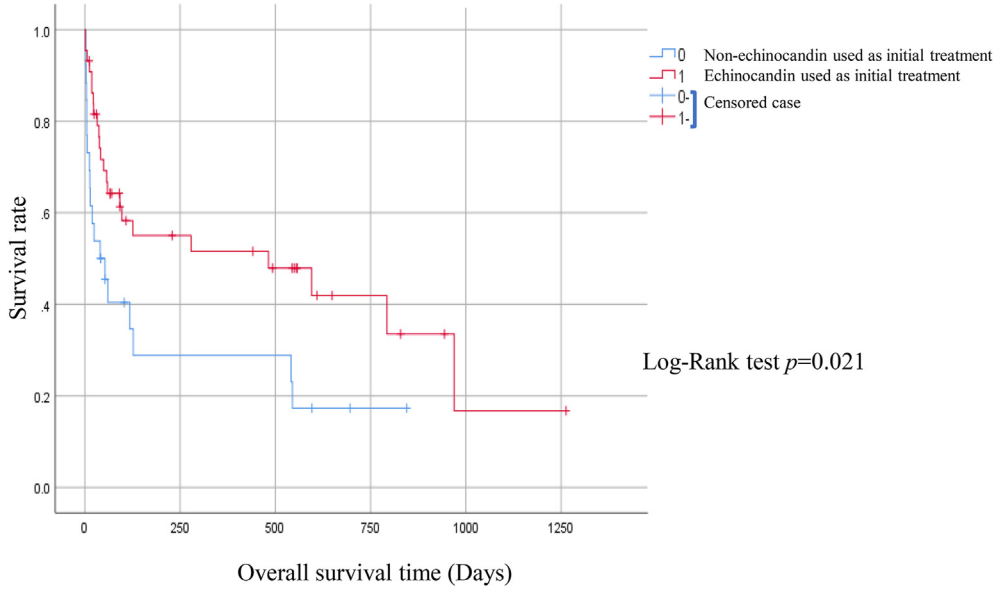

Figure 2. Shows overall survival according to echinocandin used (red line) and non-echinocandin used group (blue line).

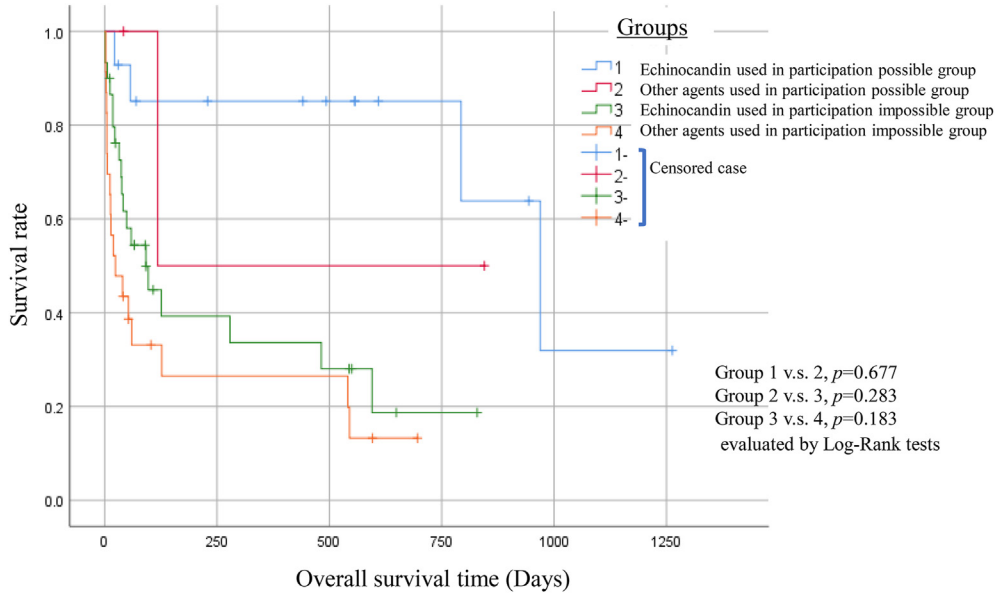

Figure 3. Shows overall survival according to echinocandin used in participation possible (red line), other agents used in participation possible (blue line), echinocandin used in participation impossible (green line), other agents used in participation impossible group (yellow line).

Dr Kaneko,[20] only 12% of COPD patients were eligible for clinical trials on COPD. It is apparent that more patients than we expect are excluded from the clinical trials for the following reasons; dementia, some patients refusing the consent for trial or selection bias by attending physicians. We definitely consider clinical trials as one of the most important evidences for medicine. Our result is not for denying the clinical trials. We are not going to recommend physicians who really believe EBM to join the famous parachute trial.[21] We just would like to insist that physicians should understand the true nature of EBM and should practice medicine for patients in the real world. Retrospective study sometimes could be more important than clinical trials and be helpful for us.

In conclusion, only 24% of candidemia patients were eligible for the clinical trials. The remaining 76% of the patients were excluded in candidemia clinical trials. We all have to know the true nature of EBM and clinical trials. Based on these facts, physicians should practice medicine for whole patients in the real world.

There are limitations in our study. First, this is a retrospective study in a small population. Thus, there might be a bias in data selection and analysis. Second, we evaluated only patients diagnosed as candidemia by blood culture. Patients without positive blood culture of *candida* spp. were excluded in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2020.11.003.