中文題目：在急性骨髓性白血病使用 posaconazole 預防侵入性黴菌感染的臨床成效

英文題目：The real-world clinical benefit of Invasive aspergillosis prophylaxis by posaconazole in acute myeloid leukemia

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Background:

Acute myeloid leukemia (AML) is a hematological malignancy with complex disease behavior with an incidence of approximately 1.3 per 100,000 people in Taiwan. A substantial proportion of AML patients who receiving intent-to-cure therapies including induction/consolidation chemotherapies and allogeneic hematopoietic stem cell transplantation (allo-HSCT), can be cured. However, around 25% of newly diagnosed AML patients only receive best supportive care without intent-to-cure therapies due to older age and more comorbidities. During the whole course of AML treatment, various complications may occur, including opportunistic infectious diseases. Among all the infectious complications in AML, invasive aspergillosis (IA) is crucial because IA infection negatively impacts on the overall treatment outcome in AML. However, the epidemiology of IA infection in AML has changed significantly over the past two decades. A progressive reduction of IA-associated mortality in AML has been observed. One of the reasons is that increased awareness and utility of Galactomannan antigen test in serum and

bronchoalveolar lavage fluid sample enhances the diagnostic ability, resulting in more appropriate antifungal treatment. Additionally, more extensive use of prophylactic antifungal therapies may further decline the IA infection during the AML treatment.

Recently, the practice guidelines proposed by the Infectious Diseases Society of America recommended posaconazole and Voriconazole for IA prevention in AML. Comparing to fluconazole or itraconazole, posaconazole demonstrated its superiority not only in the prevention of IA but also the survival among AML patients undergoing intensive chemotherapy. In terms of Voriconazole prophylaxis, it significantly decreased the incidence of IA infection in AML patients receiving remission-induction chemotherapy. However, the survival benefit was not analyzed.

Posaconazole antifungal prophylaxis in AML patients undergoing induction chemotherapy has been a standard of care in our institution since January 2012. However, it is not clear whether this prophylactic strategy really reduces the incidence of IA infection and further improves the overall survival in the real-world setting. Therefore, we conducted this retrospective study to address this question.

Methods:

Medical records of 323 consecutive adult AML patients diagnosed in Taichung Veterans General Hospital from January 2005 to May 2019 were retrospectively

reviewed. Patients who did not receive intent-to-cure induction therapy (n = 99) and those without regular follow-up (n = 16) were excluded. Finally, a total of 208 patients were analyzed. The median age of this study cohort was 51 years. 63.5% (132/208) of patients achieved CR by the first induction chemotherapy. 68 of the 208 (32.7%) patients have received allo-HSCT. The incidence of IA during the whole course of treatments was 26.4% (55/208). To investigate the impact of posaconazole prophylaxis, these 208 patients were further stratified into posaconazole antifungal prophylaxis group (n = 58) and no antifungal prophylaxis group (n = 150) according to their antifungal prophylaxis intervention during their first remission induction chemotherapy. The age (p = 0.808), gender (p = 0.503), and percentage of having received allo-HSCT (p = 0.501) were not significantly different between these two groups of patients. However, patients in the no antifungal prophylaxis group had a longer median follow-up time than patients in the posaconazole antifungal prophylaxis group (20.3 vs. 10.6 months; p = 0.001) (Table 1). The Institutional Review Board of Taichung Veterans General Hospital approved this study. This study was in accordance with the current version of the Helsinki Declaration.

Results:

The incidence of IA infection in the posaconazole antifungal prophylaxis and no antifungal prophylaxis groups was 19.0% and 29.3%, respectively (p = 0.129).(Table 1)

Our analysis showed that most IA infection was identified during the first induction chemotherapy or when disease relapsed (65.5%, 36/55). For risks for IA infection during the first induction chemotherapy, the univariate analysis revealed older age (HR: 1.01; 95% CI: 1.00–1.03; p = 0.033) and first induction chemotherapy failure (HR: 1.72; 95% CI: 1.16–2.55; p = 0.007) were associated with more IA infections. The multivariate analysis further validated that first induction chemotherapy failure was the only parameter associated with more IA infections during the first induction therapy. (HR: 1.66; 95% CI: 1.11–2.47; p = 0.013) The overall survival was comparable among patients with posaconazole antifungal prophylaxis and patients without any antifungal prophylaxis during their first induction chemotherapy. (OS : 48.3% and 37.3%, respectively; p = 0.150) (Table 1) In terms of the survival time, the median overall survival time among patients with posaconazole antifungal prophylaxis and patients without any antifungal prophylaxis was 514 (95% for the median: 270-1602) and 689 (95% for the median: 423-1243) days, respectively (p = 0.454).

Conclusion:

In summary, our study demonstrated that induction failure was the most critical factor for IA infection in AML. Compared with no systemic antifungal prophylaxis, neither the chance of IA infection nor the overall survival could be improved by

posaconazole prophylaxis in a real-world setting. Prospective studies with large numbers of patients are needed to validate our data. Finding an effective therapeutic strategy to obtain the best chance of CR without relapse remains fundamental for reduction of IA infection during AML treatments.

Table 1. Patient characteristics and outcome comparison

	Total (n = 208)		Posaconazole antifungal prophylaxis (n = 58)		No antifungal prophylaxis (n = 150)		p-value
Age, median, years (range)	51	21-79	52	23-73	51	21-79	0.808 *
Gender, n (%)							0.503 §
Male	116	(55.8)	35	(60.3)	81	(54.0)	
Female	92	(44.2)	23	(39.7)	69	(46.0)	
Disease status after 1st induction chemotherapy, n (%)							1.000 §
CR	132	(70.6)	36	(70.6)	96	(70.6)	
Non-CR	55	(29.4)	15	(29.4)	40	(29.4)	
Follow-up months, median (range)	15.9	0.1-177.4	10.6	0.5-53.4	20.3	0.1-177.4	0.001 *
Allogeneic HSCT, n (%)	68	(32.7)	21	(36.2)	47	(31.3)	0.501 §
Invasive aspergillosis infection, n (%)	55	(26.4)	11	(19.0)	44	(29.3)	0.129 §
Types of aspergillosis infection, n (%)							0.574 §
Proven	4	(1.9)	0	(0.0)	4	(2.7)	
Probable	15	(7.2)	3	(5.2)	12	(8.0)	
Possible	36	(17.3)	8	(13.8)	28	(18.7)	
Timing of aspergillosis infection, n (%)							0.863 §
At diagnosis	1	(0.5)	0	(0.0)	1	(0.7)	
During first induction therapy	23	(11.1)	4	(6.9)	19	(12.7)	
During consolidation therapy	6	(2.9)	1	(1.7)	5	(3.3)	
At relapse	13	(6.3)	2	(3.4)	11	(7.3)	
After allogeneic HSCT	3	(1.4)	1	(1.7)	2	(1.3)	
Others	9	(4.3)	3	(5.2)	6	(4.0)	
Survival, n (%)							0.150

							[§]
Yes	84	(40.3)	28	(48.3)	56	(37.3)	
No	124	(59.6)	30	(51.7)	94	(62.7)	
Causes of death (n = 124)							0.644 [§]
Acute myeloid leukemia	87	(70.2)	20	(66.7)	67	(71.3)	
Induction death	21	(13.8)	7	(23.3)	14	(14.9)	
Sepsis	2	(1.6)	1	(3.3)	1	(1.1)	
Aspergillosis	1	(0.8)	0	(0.0)	1	(1.1)	
Allo-HSCT related	9	(7.3)	2	(6.7)	7	(7.4)	
Others	4	(3.2)	0	(0.0)	4	(4.3)	

*Mann–Whitney U test; [§]Chi-Square test

CR: complete remission; HSCT: hematopoietic stem cell transplantation