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Risk factors for thrombocytopenia and analysis of time to platelet transfusion after azacitidine treatment

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The use of azacitidine (AZA) has been known to lead to a high incidence of hematotoxic adverse events. The aims of this study were to identify the risk factors for thrombocytopenia after the administration of AZA and to analyze time to the initial platelet transfusion. Sixty-two patients with myelodysplastic syndrome (MDS), who were treated with AZA in Gifu Municipal Hospital between March 2012 and June 2020, were included in this study. The risk factors for thrombocytopenia were identified using univariate analysis of patient characteristics, disease type, and laboratory values immediately before the start of treatment. Variables with p<0.2 identified in the univariate analysis were used as independent variables in the multivariate analysis. This analysis identified "creatinine clearance (CCr) <60 mL/min" as a significant factor (odds ratio, 4.790; 95% confidence interval [CI], 1.380-16.70; p=0.014). Subsequently, time in days to the initial platelet transfusion after the initial administration of AZA was analyzed using the log-rank test. The overall median time in days to platelet transfusion was 370 days. The log-rank test was used to determine the influence of patient characteristics, disease type, and laboratory values immediately before the start of treatment. The subsequent Cox proportional hazard regression analysis using variables with p<0.2 as independent variables identified "hemoglobin (Hb) <8.0 g/dL" as a significant factor (hazard ratio, 2.143; 95% CI, 1.001-4.573; p=0.048). The results of this study led to the following clinical implications: first, patients with CCr of <60 mL/min at the start of treatment should be treated with caution due to the risk of thrombocytopenia. Second, patients with Hb of <8.0 g/dL at the start of treatment may require platelet transfusion in the early stage of treatment.

1. Introduction

Myelodysplastic syndrome (MDS) is a clonal myeloid stem cell disorder with cytopenia resulting from impaired hematopoiesis (Adès et al. 2014). Azacitidine (AZA) has been used in the treatment of MDS; AZA is incorporated into the patients' DNA and RNA, showing a cytotoxic effect mainly by inhibiting protein synthesis (Hollenbach et al. 2010).

The efficacy of AZA as a drug for MDS has been established in clinical trials. Meanwhile, many studies reported hematologic adverse events after AZA treatment (Fenaux et al. 2009; Itzykson et al. 2011; Silverman et al. 2002, 2011). Practical recommendations for the management of adverse events included transfusion of red blood cells and platelets as needed if blood values do not return to normal (Götze et al. 2010). Nevertheless, to our knowledge, no studies have identified risk factors for hematologic adverse events. Therefore, the aim of this study was to identify the risk factors for thrombocytopenia to prevent thrombocytopenia-related symptoms of prolonged or excessive bleeding after the administration of AZA. In the study, the primary endpoints were risk factors for thrombocytopenia, whereas the secondary endpoint was time to platelet transfusion.

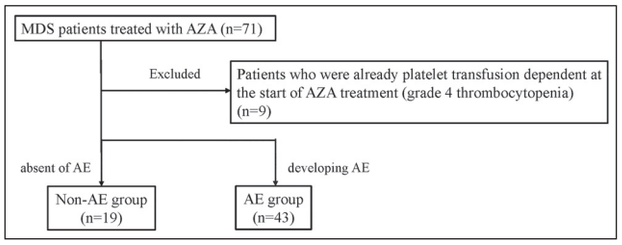

Fig. 1: Flow chart of study participants. AZA, azacitidine; AE, adverse events

2. Investigations and results

2.1. Patient characteristics

The patient characteristics of 62 patients (after excluding 9 patients with adverse events of grade 4 thrombocytopenia at the start of AZA treatment from the initial 71 patients) are shown in Fig. 1. Median (interquartile range) patient age was 72.8 (68.0-78.0) years and there were 12 women and 50 men (Table 1).

Table 1: Patient characteristics

Characteristics	Number of patient (n=62)	%
Age, years		
Median (Interquartile range)	72.8 (68.0-78.0)	
Gender		
Female	12	19.4

Male	50	80.6
ECOG PS		
0-1	54	87.1
≥ 2	8	12.9
FAB Classification		
RA	1	1.6
RARS	10	16.1
RAEB	41	66.1
CMML	2	3.2
RAEB-T	8	12.9
IPSS-R		
Low	1	1.6
Intermediate	11	17.7
High	36	58.1
Very High	14	22.6

PS; Performance status (ECOG). FAB classification; French-American-British classification. RA; Refractory anemia. RARS; Refractory anemia with ring sideroblasts. RAEB; Refractory anemia with excess blasts. RAEB-T; Refractory anemia with excess blasts in transformation. CMML; Chronic myelomonocytic leukemia. IPSS-R; Revised International Prognostic Scoring System.

2.2. Analysis of risk factors for thrombocytopenia

The adverse and non-adverse event groups consisted of 43 patients (69.4%) and 19 patients (30.6%), respectively. Multivariate analysis was performed using the presence or absence of adverse events as a dependent variable and variables with p<0.2 identified in the univariate analysis (i.e., the International Prognostic Scoring System-Revised [IPSS-R], lactate dehydrogenase [LD], and CCr) as independent variables. The analysis identified "CCr<60 mL/min" as a significant factor (odds ratio [OR], 4.790; 95% confidence interval [CI], 1.380-16.70; p=0.014) (Table 2).

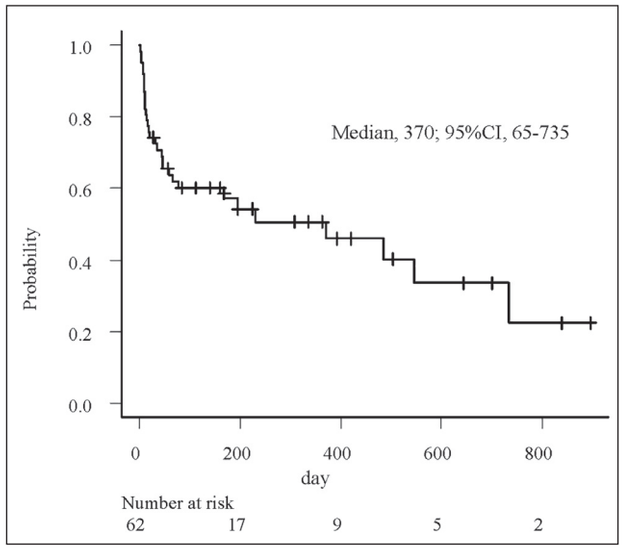

Fig. 2: Analysis of time to platelet transfusion. The curve was created using the Kaplan-Meier method and the log-rank test. The y-axis represents the non-completion rate of platelet transfusion, whereas the x-axis represents the number of days.

2.3. Analysis of time to platelet transfusion

The overall median time in days to platelet transfusion was 370 days (95% CI, 65-735 days) (Fig. 2). The non-completion rate of platelet transfusion was 74.2% (95% CI, 0.614-0.833) at the end of one cycle (28 days) and 65.6% (95% CI, 0.522-0.760) at the end of two cycles (56 days), respectively.

Using variables with p<0.2 (the Eastern Clinical Oncology Group (ECOG) performance status [PS], IPSS-R, serum albumin [ALB], and hemoglobin [Hb]) in the univariate analysis (log-rank test), the multivariate Cox proportional hazard regression analysis identified "Hb<8.0 g/dL" as a significant factor (hazard ratio [HR], 2.143; 95% CI, 1.001-4.573; p=0.048) (Table 3 and Fig. 3).

Table 2: Analysis of risk factors of adverse events

	Univariate analysis			Multivariate analysis	
Total patients (n=62)	Adverse event (-) (n=19)	Adverse event (+) (n=43) (Minimum PLT ≥ Grade 3) and (ΔGrade ≥ 1)	p-value	OR (95%CI)	p-value
Gender					
Female	2 (10.5%)	10 (23.3%)	0.313		
Male	17 (89.5%)	33 (76.7%)			
Age					
< 65 (year)	2 (10.5%)	6 (14.0%)	1.000		
≥ 65	17 (89.5%)	37 (86.0%)			
ECOG PS					
0-1	18 (94.7%)	36 (83.7%)	0.416		
≥ 2	1 (5.3%)	7 (16.3%)			

FAB classification					
RA, RARS	5 (26.3%)	6 (14.0%)	0.288		
RAEB, CMML, RAEB-T	14 (73.7%)	37 (86.0%)			
IPSS-R					
Very high	2 (10.5%)	12 (27.9%)	0.192	3.760 (0.693-20.40)	0.125
High, Intermediate, Low	17 (89.5%)	31 (72.1%)			
ALB					
< LLN (4.1 g/dL)	6 (31.6%)	20 (46.5%)	0.403		
≥ LLN	13 (68.4%)	23 (53.5%)			
ALT					
< ULN (male, 42; female, 23 [U/L])	17 (89.5%)	36 (83.7%)	0.709		
≥ ULN	2 (10.5%)	7 (16.3%)			
AST					
< ULN (30 U/L)	16 (84.2%)	37 (86.0%)	1.000		
≥ ULN	3 (15.8%)	6 (14.0%)			
T-BIL					
< ULN (1.5 U/L)	18 (94.7%)	40 (93.0%)	1.000		
≥ ULN	1 (5.3%)	3 (7.0%)			
γ-GT					
< ULN (male, 64; female, 32 [U/L])	17 (89.5%)	39 (90.7%)	1.000		
≥ ULN	2 (10.5%)	4 (9.3%)			
LD					
≥ ULN (222 U/L)	6 (31.6%)	22 (51.2%)	0.177	3.260 (0.911-11.70)	0.069
< ULN	13 (68.4%)	21 (48.8%)			
WBC					
< 2000 (μL)	12 (63.2%)	31 (72.1%)	0.555		
≥ 2000	7 (36.8%)	12 (27.9%)			
Hb					
< 8.0 (g/dL)	5 (26.3%)	17 (39.5%)	0.395		
≥ 8.0	14 (73.7%)	26 (60.5%)			
BUN					
< ULN (20 mg/dL)	17 (89.5%)	38 (88.4%)	1.000		
≥ ULN	2 (10.5%)	5 (11.6%)			
CCr					
< 60 (mL/min)	7 (36.8%)	29 (67.4%)	0.030	4.790 (1.380-16.70)	0.014*
≥ 60	12 (63.2%)	14 (32.6%)			

OR; Odds ratio. 95% CI; 95% confidence interval. Grade; Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. ΔGrade; The difference between the platelet grade immediately before AZA administration and the grade at the time of the lowest platelet count. PS; Performance status (ECOG). ALB; Serum albumin. ALT; Alanine aminotransferase. AST; Aspartate aminotransferase. T-BIL; Total bilirubin. γ-GT; γ-glutamyl transpeptidase. LD; Lactate dehydrogenase. WBC; White blood cell count. Hb; Hemoglobin. BUN; Blood urea nitrogen. CCr; Creatinine clearance. FAB classification; French-American-British classification. RA; Refractory anemia. RARS; Refractory anemia with ring sideroblasts. RAEB; Refractory anemia with excess blasts. CMML; Chronic myelomonocytic leukemia. RAEB-T; Refractory anemia with excess blasts in transformation. IPSS-R; Revised International Prognostic Scoring System. ULN; Upper limit of normal value. LLN; Lower limit of normal value. *; $p<0.05$.

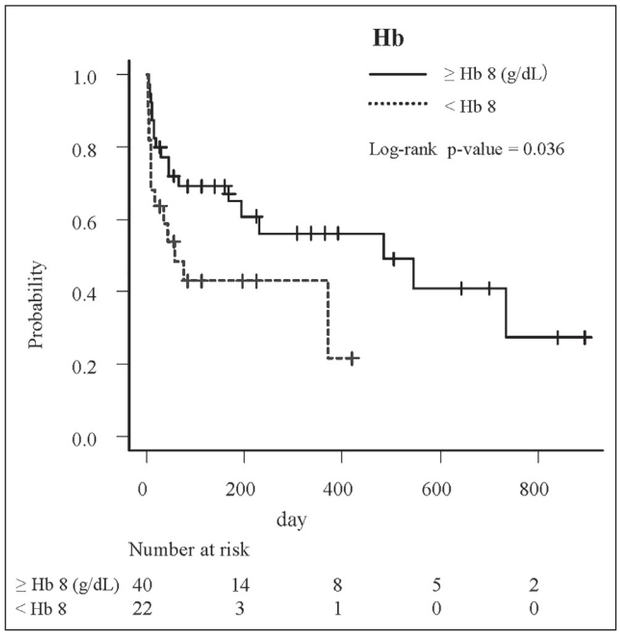

Fig. 3: A comparison of time to platelet transfusion between two groups divided by the cut-off value of hemoglobin (8 g/dL). The curve was created using the Kaplan-Meier method and the log-rank test. The y-axis represents the non-completion rate of platelet transfusion, whereas the x-axis represents the number of days.

3. Discussion

The aims of this study were to identify the risk factors for thrombocytopenia and analyze time to the initial platelet transfusion in MDS patients treated with AZA. Many studies in other countries reported thrombocytopenia after AZA treatment (Fenaux et al. 2009; Itzykson et al. 2011; Silverman et al. 2002, 2011). A Japanese study also reported similar findings (Uchida et al. 2011). Furthermore, it must be noted that a study in another country reported severe bleeding symptoms (Silverman et al. 2006). However, to our knowledge, the current study is the first study in a clinical setting that identified the risk factors for thrombocytopenia after AZA treatment and calculated time to platelet transfusion.

The multivariate analysis identified "CCr<60 mL/min" as a risk factor of thrombocytopenia, a primary endpoint of this study. Regarding the relationship between adverse events and renal function in the administration of AZA, Douvali et al. (2013) found that the administration of AZA in patients with renal failure is possible, but that it may increase the incidence of toxicity. Moreover, Laille et al. (2014) also found the adverse effects of AZA in patients with severe renal dysfunction. However, both studies examined patients with severe renal dysfunction. Therefore, it is difficult to compare their findings with ours. In addition, Batty et al. (2010) reported a higher incidence of hepatotoxicity in patients treated with methylation inhibitors such as AZA. However, their study included patients with acute or chronic myeloid leukemia. Therefore, it is difficult to compare their findings with ours. In the current study, older adult patients were examined in clinical practice. Our findings in the current study are clinically significant in that we identified "CCr<60 mL/min" as a risk factor of thrombocytopenia.

Table 3: Analysis of risk factors for platelet transfusion

	Univariate analysis		Multivariate analysis	
Total patients (n=62)	Median platelet transfusion (day)	p-value	HR (95%CI)	p-value
Gender				
Female	45	0.223		
Male	485			
Age				
≥ 65 (year)	231	0.648		
< 65	370			
ECOG PS				
≥ 2	45	0.108	2.068 (0.743-5.758)	0.164
0-1	370			
FAB classification				
RAEB, CMML, RAEB-T	231			
RA, RARS	370			
IPSS-R				
Very high	45	0.037	1.929 (0.867-4.295)	0.108
High, Intermediate, Low	485			
ALB				
< LLN (4.1 g/dL)	195	0.055	1.607 (0.700-3.688)	0.263
≥ LLN	485			
ALT				

≥ ULN (male, 42; female, 23 [U/L])	231	0.682		
< ULN	370			
AST				
≥ ULN (30 U/L)	43	0.227		
< ULN	485			
T-BIL				
≥ ULN (1.5 U/L)	65	0.818		
< ULN	370			
γ-GT				
≥ ULN (male, 64; female, 32 [U/L])	207	0.633		
< ULN	485			
LD				
≥ ULN (222 U/L)	231	0.633		
< ULN	370			
WBC				
< 2000 (μL)	231	0.854		
≥ 2000	485			
Hb				
< 8.0 (g/dL)	58	0.036	2.143 (1.001-4.573)	0.048*
≥ 8.0	485			
BUN				
≥ ULN (20 mg/dL)	195	0.411		
< ULN	370			
CCr				
< 60 (mL/min)	195	0.991		
≥ 60	370			

ALB; Serum albumin. HR; Hazard ratio. 95% CI; 95% confidence interval. PS; Performance status (ECOG). ALT; Alanine aminotransferase. AST; Aspartate aminotransferase. T-BIL; Total bilirubin. γ-GT; γ-glutamyl transpeptidase. LD; Lactate dehydrogenase. WBC; White blood cell count. Hb; Hemoglobin. BUN; Blood urea nitrogen. CCr; Creatinine clearance. FAB classification; French-American-British classification. RA; Refractory anemia. RARS; Refractory anemia with ring sideroblasts. RAEB; Refractory anemia with excess blasts. CMML; Chronic myelomonocytic leukemia. RAEB-T; Refractory anemia with excess blasts in transformation. IPSS-R; Revised International Prognostic Scoring System. ULN; Upper limit of normal value. LLN; Lower limit of normal value. *; $p<0.05$.

This suggests that monitoring pre-treatment CCr may be used as a screen prior to prescribing AZA or similar medications to identify patients with a higher risk and prevent adverse events.

Furthermore, the overall median time in days to platelet transfusion (secondary endpoint) was 370 days. The non-completion rate of platelet transfusion was 74.2% at the end of one cycle and 65.6% at the end of two cycles, respectively, showing that some patients required platelet transfusion in the early stage of treatment. It has been reported that, in many cases, Patients with MDS are already platelet transfusion dependent at the start of treatment (Itzykson et al. 2011; Silverman et al. 2011). Despite excluding platelet transfusion dependent patients at the start of this study, some patients required platelet transfusion from the early stage of AZA treatment. Santini et al. (2010) performed two large-scale phase III trials of hematologic adverse events and found that continued AZA treatment reduced the incidence of thrombocytopenia. Their findings suggest that appropriate management of platelet count and Hb levels in the early stage of treatment prevents subsequent hematotoxicity. Furthermore, continued treatment has been reported to increase the efficacy of AZA (Fenaux et al. 2009; Silverman et al. 2006; Usami et al. 2020). Close monitoring of hematotoxicity in the early stage of treatment may be important to prevent adverse events and improve the efficacy of the treatment. In the current study, multivariate Cox proportional hazard analysis was performed using variables with $p<0.2$ that were identified in the univariate analysis (i.e., PS, IPSS-R, ALB, and Hb). As a result, the analysis identified "Hb<8.0 g/dL" as a significant factor. In other words, this suggests that patients with Hb of <8.0 g/dL may require platelet transfusion in the early stage of treatment. The results also suggest that transfusion of red blood cells and platelets requires close monitoring for hematotoxicity from the early stage of AZA treatment.

This study is clinically significant in that it identified risk factors for thrombocytopenia and analyzed time to platelet transfusion in a clinical setting. However, the current study has the limitation that it was a single-center retrospective study with a small sample size. Although this study may be useful as a pilot study, future research should include prospective studies targeting multiple facilities.

4. Experimental

4.1. Participants

Patients with myelodysplastic syndrome (MDS) who were treated with AZA in the Department of Hematology, Gifu Municipal Hospital between March 2012 and June 2020 were sequentially sampled. Sixty-two patients (50 men and 12 women) were included in this study after applying the exclusion criterion. The exclusion criterion was patients who were platelet transfusion dependent at the start of AZA treatment.

4.2. Endpoints and adverse events

Patient characteristics were analyzed (i.e., age, gender, PS, the French-American-British [FAB] Classification, and IPSS-R).

Immediately before the start of treatment the following laboratory test variables were examined: ALB, alanine aminotransaminase (ALT), aspartate transferase (AST), total bilirubin (T-BIL), γ-glutamyl transpeptidase (γ-GT), LD, white blood cell count (WBC), Hb, blood urea nitrogen (BUN), and creatinine clearance (CCr [Cockcroft-Gault formula]) (Cockcroft et al. 1976).

The following test variables of thrombocytopenia were examined: 1) platelet count immediately before the administration of AZA (Pre-PLT); 2) the lowest platelet count before the discontinuation or postponement of AZA treatment or platelet transfusion (Min-PLT); 3) time in days to the initial platelet transfusion after the initial administration of AZA; and 4) time in days to discontinuation or modification of AZA treatment. The above variables were retrospectively examined using electronic medical records. Regarding the adverse events, Pre-Grade was defined as "Pre-PLT grade," whereas Min-Grade was defined as "Min-PLT grade." The adverse event group was defined as patients with ΔGrade (grade change from Pre-Grade to Min-Grade) of ≥1 and Min-Grade of ≥3, whereas the non-adverse event group was defined as the remaining patients. The grade of adverse events was determined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (U.S. Department of Health and Human Services 2017).

4.3. Statistical analysis

4.3.1. Analysis of the risk factors for thrombocytopenia

The following binary variables were used in the analysis: age (<65 or ≥65 years, which is based on the definition in Japan that people aged 65 and over are the elderly), the ECOG-PS (0, 1, or ≥2), the FAB classification ("refractory anemia [RA] or refractory anemia with ring sideroblasts [RARS]" or "refractory anemia with excess blasts [RAEB], chronic myelomonocytic leukemia [CMML], or RAEB in transformation [RAEB-T]"), and IPSS-R ("very high" or "high, intermediate, or low").

The laboratory test variables were respectively converted to binary variables (presence or absence of adverse events) using the upper limit of normal value (ALT, AST, T-BIL, γ-GT, LD, and BUN) or the lower limit of normal value (ALB) as the cut-off point. WBC and Hb were respectively converted to binary variables using grade 3 according to the CTCAE as the cut-off point. CCr was converted to a binary variable (<60 or ≥60 mL/min) using the normal value (≥60 mL/min) as the cut-off point according to the "Evidence-based Clinical Practice Guidelines for Chronic Kidney Disease 2018 (Japanese Society of Nephrology)."

Patients were divided into two groups: the adverse event and non-adverse event groups. Variables with $p<0.2$ that were identified in the univariate analysis (Fisher's exact test) were used as independent variables in the multivariate analysis (multiple logistic regression analysis).

4.3.2. Analysis of time to platelet transfusion

Variables with $p<0.2$ that were identified in the univariate analysis (using the Kaplan-Meier method and the log-rank test) were used in the multivariate Cox proportional hazard regression analysis.

All statistical analyses, including (1) factor analysis of thrombocytopenia and (2) time analysis of platelet transfusion, were performed using Easy R (EZR) version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan [Kanda et al. 2013]). $P<0.05$ was considered statistically significant.

4.4. Ethical considerations

This study was conducted in accordance with the ethical guidelines of the Helsinki Declaration with the approval of the ethics committees of Gifu Municipal Hospital (registration number: 653) and Gifu Pharmaceutical University (approval number: 2-22). The participants were given the option to opt out of the study.

Conflicts of interest: None declared.

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