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Procalcitonin elevation in febrile recipients during pre-transplant conditioning with anti-thymocyte globulin

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Abstract

Infection is a major contributor to non-relapse mortality in allogeneic hematopoietic stem cell transplantation (allo-HSCT). Detecting infectious diseases in febrile patients during pretransplant conditioning is crucial for subsequent transplant success. Procalcitonin (PCT) is an auxiliary diagnostic marker of severe bacterial infections and has been proposed as a useful predictor of infection in patients undergoing allo-HSCT. Pre-transplant use of anti-thymocyte globulin (ATG) can cause side effects, such as fever and hypotension, which must be distinguished from infectious diseases. Although ATG administration may increase PCT levels, data on PCT levels in febrile patients after ATG administration are limited. Furthermore, no studies have compared PCT levels during allo-HSCT conditioning using ATG or non-ATG regimens. To investigate whether ATG increases PCT levels during febrile episodes in pre-transplant conditioning and whether PCT could be used to discriminate infections during this period, we analyzed 17 ATG and 59 non-ATG patients with fever and who underwent PCT level measurements during pre-transplant conditioning. Our findings revealed that ATG administration was the only significant factor that increased PCT positivity during fever (p = 0.01). In contrast, infectious diseases did not affect PCT positivity in the ATG group (p = 0.24). Furthermore, bloodstream infection was a significant risk factor for PCT positivity in patients who received non-ATG regimens (p < 0.01). Incorporating PCT levels into the diagnostic workup for infectious diseases requires careful consideration, particularly for patients receiving ATG regimens.

Key words Procalcitonin, Febrile, ATG

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Introduction

Infection is a significant factor for non-relapse mortality during allogeneic hematopoietic stem cell transplantation (allo-HSCT)[1]. During the pre-transplant conditioning stage of allo-HSCT, the risk of infection increases, and the presence of infection during this stage affects subsequent transplant success[2]. Therefore, the early detection and appropriate treatment of infectious diseases during the conditioning stage are critical for successful transplantation.

In 1992, procalcitonin (PCT) was identified by Nylen as a marker of severe inflammation[3]. In severe bacterial or fungal infections, pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), are produced, and PCT is secreted into the blood by various organs throughout the body[4]. PCT is widely used as an auxiliary diagnostic marker for severe bacterial infections. PCT levels are also elevated in patients with hematological or immunosuppressive disorders, both before and after allo-HSCT, and several studies have suggested that PCT can be used to predict infections in this setting[5-8]. However, there have been some negative reports[9, 10], and opinions on this issue are inconsistent.

Antithymocyte globulin (ATG) is commonly used as a conditioning regimen to prevent graft rejection and

graft-versus-host disease (GVHD) by removing the donor lymphocytes[11]. However, it can cause systemic reactions, such as fever and hypotension[12]. Therefore, it is important to distinguish these symptoms from those of infectious diseases. Although ATG administration in allo-HSCT conditioning regimens is known to increase PCT levels[13, 14], the PCT levels in febrile patients following ATG administration have not yet been reported. Furthermore, no study has directly compared the increase in PCT levels during conditioning for allo-HSCT and its risk factors between ATG and non-ATG regimens.

To investigate whether ATG administration could increase PCT levels during febrile episodes in the context of pretransplant conditioning and whether PCT could be used to discriminate infections during this period, we retrospectively analyzed 76 patients who developed febrile episodes during pretransplant conditioning and had their PCT levels measured at our institution.

Patients and Methods

Patients and clinical data

Between January 2012 and September 2014, when ATG was actively used at our institution, 94 patients underwent allo-HSCT at the Kyushu University Hospital. Among them, 76 patients who had no fever or documented infections (DIs) before conditioning (ATG administration for patients on an ATG regimen) and who developed fever followed by PCT measurements during conditioning for allo-HSCT were retrospectively analyzed. For all 76 patients, complete clinical data, such as age, sex, donor stem cell source, primary disease, disease status prior to allo-HSCT, and conditioning regimen, were collected (**Table 1**). Reduced-intensity conditioning was defined as a regimen with total body irradiation of less than 8 Gy, a melphalan dose of 140 mg/sqm or less, and a busulfan dose of 8 mg/kg or less administered orally or intravenously at equivalent dosages[15]. This retrospective study was approved by the Institutional Review Board of Kyushu University Hospital (No. 22327-00). The Institutional Review Board approved this study with opt-out consent.

Definition of febrile episodes

Fever was defined as an axillary body temperature of 37.5° C or more according to the diagnostic criteria for febrile neutropenia. Except for bloodstream infections (BSIs), documented infections DIs were defined as microbiologically documented or presumed infections based on clinical and/or radiological findings[7]. BSIs were analyzed independently from general "documented infection" in this study. BSI was identified based on at least two consecutive positive blood cultures.

Table 1. Patients' characteristics

Procalcitonin (negative/positive)	48/28
Median age [years (range)]	48 (17-69)
Sex (male/female)	39/37
Stem cell source (BM/PB)	38/38
Diagnosis	
AML + MDS	34
ALL	13
NHL	24
HD	1
AA	2
other	2
Disease status (non-CR/CR)	47/29
Conditioning regimen	
RIC/MAC	61/15
TBI (Yes/No)	43/33
CY (Yes/No)	20/56
BU (Yes/No)	14/62
Flu (Yes/No)	59/17
Mel (Yes/No)	38/38
Ara-C (Yes/No)	14/62
ATG (Yes/No)	17/59

BM, bone marrow; PB, peripheral blood; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; AA, aplastic anemia; CR, complete remission; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; CY, cyclophosphamide; BU, busulfan; Flu, fludarabine; Mel, melphalan; Ara-C, cytarabine; ATG, antithymocyte globulin.

Laboratory data measurement and assessment

Blood samples were obtained within 24 h (on the same day or the next calendar day) after the fever reached 37.5° C or higher to measure the levels of PCT and other laboratory parameters. Serum PCT levels were measured using the Accuraseed PCT assay (Wako Junyaku, Osaka, Japan). The cutoff value was 0.5 ng/mL, and the results were classified as negative (<0.5 ng/mL) or positive (≥0.5 ng/mL) according to the manufacturer's recommendations.

Statistical analysis

Fisher's exact test or the chi-square test was used to compare categorical variables, while the Kruskal-Wallis *U* test was used to compare continuous variables. Univariate analysis was performed using logistic or exact logistic regression analysis, and parameters with *p*-values less than 0.10 were re-evaluated using multivariate analysis. Multivariate analysis was performed using logistic regression with Firth's bias reduction. A *p*-value less than 0.05 was considered statistically. Statistical analyses were performed using EZR[16] software and GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA).

Results

PCT positivity upon fever during the conditioning stage in non-ATG versus ATG regimens

Among the 76 patients who developed fever during the conditioning stage and had their PCT levels measured, 48 were PCT-negative and 28 were PCT-positive (**Table 1**). Although it is recognized that ATG administration in conditioning regimens for allo-HSCT leads to elevated PCT levels[13, 14], there is a lack of reported data on PCT levels in "febrile patients" following ATG administration. Therefore, the impact of ATG use on PCT positivity during pre-transplantation procedures in the context of fever was investigated. It was found that the non-ATG group (n = 59) had PCT levels ranging from 0.04 to 9.60 ng/mL (median, 0.12 ng/mL), whereas the ATG group (n = 17) had PCT levels ranging from 0.10 to 14.58 ng/mL (median, 1.60 ng/mL), indicating that PCT levels were significantly increased with an ATG-containing regimen ($p < 0.0001$) (**Figure 1**).

We further analyzed whether the patients' clinical characteristics had an impact on PCT positivity upon fever onset during the conditioning stage in the non-ATG and ATG groups. Of the 59 patients who received non-ATG regimens, 44 were PCT-negative and 15 were PCT-positive. When clinical characteristics were compared, no significant differences in PCT positivity were observed (**Table 2**). Of the 17 patients who received an ATG regimen, four were PCT-negative and 13 were PCT-positive. When clinical characteristics were compared, no significant differences in PCT positivity were observed (**Table 2**).

BSI poses a risk for PCT positivity in patients treated with a non-ATG regimen

PCT is used as a marker for DIs, including BSI and sepsis, in many clinical cases[4], and it is important to differentiate infectious diseases when PCT is positive during allo-HSCT conditioning. Therefore, we investigated the effect of infectious disease development on PCT positivity upon fever during conditioning for all-HSCT in the non-ATG and ATG groups.

First, we conducted a comprehensive analysis of DIs and BSIs as indicators of infectious diseases. Among the 44 patients with a negative PCT result in the non-ATG regimen group, infection occurred in three cases, while among the 15 cases with a positive PCT result, eight cases developed infections ($p = 0.0003$), indicating a significant association between PCT positivity and infection in this group. In contrast, in the ATG regimen group, among the four patients with a negative PCT result, one developed infection, and among the 13 patients with a positive PCT result, two developed infection ($p = 1.00$), suggesting a mixture of infectious and non-infectious cases in the ATG regimen group (**Figure 1**).

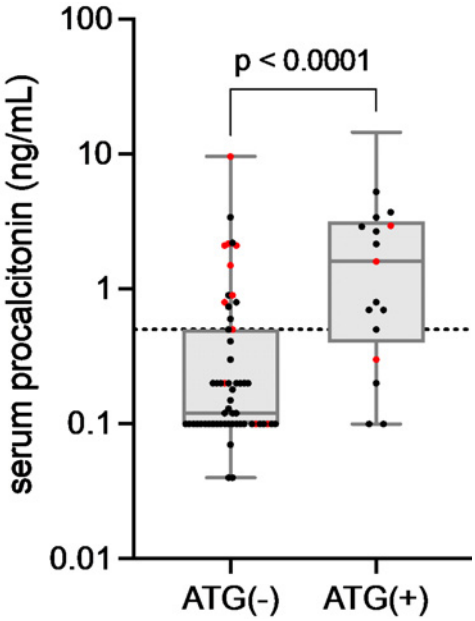

Figure 1. Serum procalcitonin levels upon fever
Procalcitonin levels of each patient without and with anti-thymocyte globulin (ATG)-containing regimen are shown. Box and whisker plots display the median, 25th and 75th percentiles of the distribution (box) and whiskers extend to 5th and 95th percentiles. Red dots indicate the patients who developed any documented infectious diseases during conditioning regimen.

These data were reevaluated based on the use of ATG and the presence of infectious diseases. As shown in **Figure 2**, the PCT levels were significantly higher in the non-ATG group with infectious diseases, the ATG group without infectious diseases, and the ATG group with infectious diseases than in the non-ATG group without infectious diseases. However, no significant differences in PCT levels were observed among the three groups.

We conducted an analysis to differentiate between infectious diseases, DIs, and BSIs. In addition, the impact of the administered ATG dosage, C-reactive protein (CRP) levels, hepatic function, and renal function on PCT positivity was evaluated. The causative pathogens in the five BSI cases in the non-ATG group comprised two cases of *Staphylococcus epidermidis*, two cases of *Corynebacterium* species, and one case of *Enterobacter cloacae*. Additionally, in the two BSI cases in the ATG group, the pathogens were identified as *Corynebacterium jeikeium* and *Staphylococcus caprae*. CRP positivity; elevated total bilirubin, aspartate aminotransferase, or alanine aminotransferase levels; and a reduced estimated glomerular filtration rate had no significant impact on PCT positivity in the non-ATG group. Regard-

Table 2. Patients' characteristics of non-ATG and ATG groups

	non-ATG regimen					ATG regimen				
	procalcitonin		Univariate			procalcitonin		Univariate		
	negative (n=44)	positive (n=15)	odds ratio	95%CI	*p* value	negative (n=4)	positive (n=13)	odds ratio	95%CI	*p* value
Median age [years (range)]	52 (17-69)	43 (21-62)	-	-	0.09	29 (22-31)	45 (22-64)	-	-	0.14
Sex (male/female)	23/21	9/6	1.37	0.42-4.53	0.83	1/3	6/7	2.57	0.21-31.71	0.60
Stem cell source (BM/PB)	29/15	6/9	0.34	0.10-1.15	0.14	0/4	3/10	3.00	0.13-70.87	0.54
Diagnosis										
AML + MDS	20	6	1.00	reference	-	3	5	1.00	reference	-
ALL	10	1	0.33	0.34-3.16	0.65	0	2	3.18	0.12-87.92	1.00
NHL	13	8	2.05	0.58-7.29	0.42	0	3	4.45	0.17-115.13	0.49
HD	1	0	1.05	0.03-29.08	1.00	0	0	-	-	-
AA	0	0	-	-	-	0	2	3.18	0.12-87.92	1.00
other	0	0	-	-	-	1	1	0.60	0.03-13.58	1.00
Disease status (non-CR/CR)	23/21	10/5	1.83	0.54-6.22	0.50	3/1	11/2	1.88	0.12-27.80	1.00
Conditioning regimen										
RIC/MAC	30/14	13/2	3.03	0.60-15.30	0.20	4/0	13/0	3.00	0.05-174.36	1.00
TBI (Yes/No)	32/12	10/5	0.75	0.21-2.65	0.91	0/4	1/12	1.08	0.04-31.63	1.00
CY (Yes/No)	14/30	2/13	0.33	0.07-1.66	0.20	1/3	3/10	0.90	0.07-12.18	1.00
BU (Yes/No)	10/34	4/11	1.24	0.32-4.74	0.97	0/4	0/13	0.33	0.01-19.37	1.00
Flu (Yes/No)	30/14	13/2	3.03	0.60-15.30	0.20	4/0	12/1	0.93	0.03-27.12	1.00
Mel (Yes/No)	17/27	8/7	1.82	0.56-5.92	0.49	3/1	10/3	1.11	0.08-15.04	1.00
Ara-C (Yes/No)	5/39	2/13	1.20	0.21-6.95	1.00	2/2	5/8	0.63	0.07-5.97	1.00

ATG, antithymocyte globulin; BM, bone marrow; PB, peripheral blood; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; AA, aplastic anemia; CR, complete remission; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; CY, cyclophosphamide; BU, busulfan; Flu, fludarabine; Mel, melphalan; Ara-C, cytarabine; CI, confidence interval.

ing infectious diseases, while patients with BSI had significant PCT positivity, DIs other than BSI had no effect on PCT positivity in the non-ATG group (**Table 3**). In the ATG group, the administered ATG dose; CRP positivity; elevated total bilirubin, aspartate aminotransferase, or alanine aminotransferase levels; and reduced estimated glomerular filtration rate had no significant impact on PCT positivity (**Table 3**).

Discussion

In this study, we revealed that the use of an ATG regimen in pre-transplant conditioning is a risk factor for elevated PCT levels. Furthermore, while elevated PCT levels are indicators of BSI risk in patients receiving non-ATG regimens, they are not predictors of BSI or DI in those receiving ATG regimens.

Broska et al. reported that PCT levels increased 1 day after ATG administration in patients undergoing allo-HSCT conditioning, and this increase persisted for 3 days, despite the absence of any obvious infection[13]. However, only one of the 26 patients, who received ATG treatment in their study, had fever, with a 3% incidence, which is significantly lower than the reported incidence of fever above 38°C in 82.6% of patients treated with ATG during pre-transplant conditioning[17]. In clinical practice, PCT is usually measured in the presence of fever, and previous research has not revealed whether the use of ATG in pre-transplant conditioning poses a risk of PCT positivity in the presence of fever. Furthermore, it is uncertain whether becoming PCT-positive while receiving ATG treatment for fever poses a risk of infection. Therefore, we limited our analysis to patients who developed fever after receiving ATG treatment, and measured the PCT positivity rate in comparison with the PCT positivity rate I the non-ATG group to shed light on the significance of PCT positivity in ATG treatment.

With the widespread use of posttransplant cyclophosphamide (PTCy) regimens in recent years[18], the use of ATG regimens in our hospital has decreased. Given the recent progress in supportive therapies, such as antibiotics and antifungal agents, the incidence of infections may vary depending on the use of different supportive therapies. Therefore, we limited this study to cases transplanted before the introduction of the PTCy regimen in our institution and found that the PCT positivity rate was 76.5%, which was significantly higher than that in the non-ATG conditioning group during fever (25.4%).

PCT is produced in a variety of organs, including the lungs, kidneys, liver, adipose tissue, and muscles, in re-

sponse to inflammatory cytokines such as TNF-α and interleukin-6 (IL-6), which are typically released following infections[19]. While PCT levels significantly increase after ATG treatment in the context of pre-transplant conditioning[13], the mechanism underlying the lack of PCT increase in some patients remains unclear.

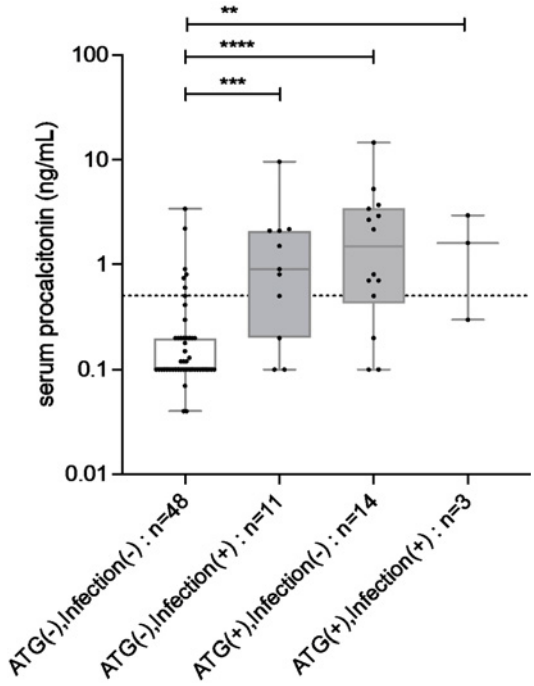

Figure 2. Serum procalcitonin levels upon fever based on the use of ATG and the presence of infectious diseases

Procalcitonin levels of each patient without and with anti-thymocyte globulin (ATG)-containing regimen and infectious diseases are shown. Box and whisker plots display the median, 25th and 75th percentiles of the distribution (box) and whiskers extend to 5th and 95th percentiles. Asterisk indicates statistical difference: $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

Kuse reported that PCT levels increased to 12.1 ± 6 ng/mL within 24 h of administering anti-thymocyte OKT3 to liver transplant patients, despite the absence of infection[20]. They suggested that the TNF-α released from necrotic tumors caused by OKT3 contributed to the increase in PCT levels. However, no correlation was found between the presence or absence of tumors (remission or non-remission) and the rate of PCT positivity following ATG administration in our study. Furthermore, Pihusch et al. reported an increase in PCT levels in patients who received ATG for GVHD prevention after HSCT, and suggested a relationship between the increase in CRP and IL-6 levels[21]. However, because these patients had previously received immunosuppressive therapy, a direct comparison with our data is difficult. Although TNF-α and IL-6 levels were not measured in our study, no significant correlation was found between the PCT positivity rate and the increase in CRP levels in the ATG group. As ATG is a polyclonal antibody[22], differences in immunogenicity between different lots may affect the extent of induction of inflammatory cytokines. ATG also contributes to the elimination of T-cells via mechanisms such as antibody-dependent cellular cytotoxicity, complement-dependent cellular cytotoxicity, and apoptosis[22]. Thus, differences in antigenicity, including genetic polymorphisms, or in the activity of residual immune cells, such as natural killer cells, may be related to the differences in PCT levels after ATG administration. Accumulating data on lot-to-lot comparisons, genetic polymorphism analyses, and residual immune cell activity analyses are necessary to clarify the mechanisms underlying the increase in PCT levels with the ATG regimen.

Notably, when fever occurs during ATG administration and PCT yields a positive result, false-positive results may occur. Nonetheless, 15% of the cases with

Table 3. Parameters associated with procalcitonin positivity

		non-ATG regimen					ATG regimen				
		procalcitonin		Univariate			procalcitonin		Univariate		
		negative (n=44)	positive (n=15)	odds ratio	95% CI	*p* value	negative (n=4)	positive (n=13)	odds ratio	95% CI	*p* value
Total ATG dosage	2.0 mg/kg	-	-	-	-	-	0	1	1.00	reference	-
	2.5 mg/kg	-	-	-	-	-	4	8	0.63	0.02-18.84	1.00
	3.0 mg/kg	-	-	-	-	-	0	4	3.00	0.03-228.66	1.00
CRP (>0.14 mg/dL)	(Yes/No)	38/6	15/0	5.23	0.28-98.63	0.32	3/1	13/0	11.57	0.38-350.10	0.26
T.Bil (>1.5 mg/dL)	(Yes/No)	2/42	2/13	3.23	0.41-25.26	0.27	0/4	0/13	0.33	0.01-19.37	1.00
AST (>30 U/L)	(Yes/No)	23/21	9/6	1.37	0.42-4.50	0.83	1/3	6/7	2.57	0.21-31.71	0.60
ALT (>42 U/L)	(Yes/No)	12/22	3/12	0.46	0.11-1.95	0.34	1/3	4/9	1.33	0.10-17.10	1.00
eGFR (<60)	(Yes/No)	4/40	5/10	5.00	1.13-22.10	0.07	0/4	6/7	7.80	0.35-173.98	0.24
BSI	(Yes/No)	0/44	5/10	46.62	2.39-910.63	<0.01	0/4	2/11	1.96	0.08-49.26	1.00
DI (except for BSI)	(Yes/No)	3/41	3/12	3.41	0.61-10.17	0.17	1/3	0/13	0.09	0.00-2.61	0.24

ATG, antithymocyte globulin; CRP, C-reactive protein; T.Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate; BSI, bloodstream infection; DI, documentaed infection; CI, confidence interval.

positive PCT results in the ATG group were attributed to BSIs in our study. Furthermore, DIs were observed in some patients, both with and without ATG use, despite no increase in PCT levels. Given the importance of promptly diagnosing and treating infections in the context of transplant therapy, physicians must exercise caution when relying heavily on PCT findings. While false positives for PCT were more prevalent in the ATG group, it is imperative to thoroughly screen for infections in patients with positive PCT outcomes. In the future, other biomarkers in addition to PCT may have potential value in the detection of infections and ATG-induced fever.

The findings of this study indicate that elevated PCT levels are not an indicator of infection in febrile recipients receiving an ATG-containing pre-conditioning regimen. However, it is worth noting that this study was retrospective and only investigated data related to fever onset. To elucidate the significance of ATG-induced PCT elevation and the associated risks of infection, a large-scale prospective study on PCT and IL-6 and TNF-α levels, as well as other relevant factors, from pre-treatment to post-ATG administration over a sufficient duration is warranted.

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Author Contributions

T.S. coordinated the project, performed the allo-SCT, designed and analyzed the data, and wrote the manuscript; M.M., T.T., Y.K., F.J., T.Y., Y.M., G.Y., S.M., T. M., and K.K. performed allo-SCT, organized patient information and reviewed the manuscript; and K.A. designed the study, reviewed the manuscript, and edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

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