Nested Case-Control Study Utilizing MID-NET®on Thrombocytopenia Associated With Pegfilgrastim in Patients Treated With Antineoplastic Agents

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Although several spontaneous case reports on the occurrence of thrombocytopenia in patients treated with human granulocyte colony-stimulating factor (G-CSF) preparations have been accumulated, its actual causality is still unclear. To investigate the association between G-CSF preparations (filgrastim, nartograstim, lenograstim, and pegfilgrastim) available in Japan and thrombocytopenia in patients treated with antineoplastic agents, a nested case-control study was conducted using the Medical Information Database NETwork (MID-NET®) with the cohort of the Japanese population taking antineoplastic agents between 2009 and 2018. A case of thrombocytopenia was defined as a patient who had decreased platelet counts (< 50,000/mm^3). We identified a maximum of 10 controls for each case matched on the index date. Adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) of thrombocytopenia for the use of G-CSF preparations compared with nonuse were estimated using conditional logistic regression. From the cohort in which 33,124 patients were included, 733 cases and 5,592 controls were identified. Compared with the nonuse of G-CSF preparations, the use of any G-CSF preparations increased the risk of thrombocytopenia (aOR: 5.7, 95% CI: 4.3-7.5). More detailed analysis showed that a distinctive increased risk was observed when pegfilgrastim was prescribed at 2–7 days before the index date (aOR: 7.4 95% CI: 2.0–28.1). Associations of the other G-CSF preparations with thrombocytopenia were unclear due to the inconsistent results among different analyses. A significantly increased risk of thrombocytopenia associated with pegfilgrastim was identified, leading to a revision of precautions in the package inserts of pegfilgrastim as a regulatory safety action.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Spontaneous case reports of severe thrombocytopenia after receiving granulocyte colony-stimulating factor (G-CSF) preparations during myelosuppressive chemotherapy have been accumulated, but the causality with G-CSF preparations is currently unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Do G-CSF preparations cause thrombocytopenia in patients treated with antineoplastic agents?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Significant risk elevation of thrombocytopenia by pegfilgrastim was observed. The risk by the other G-CSF preparations was unclear due to the inconsistent results among different analyses.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ More attention on thrombocytopenia may be necessary during treatment with pegfilgrastim.

Human granulocyte colony-stimulating factor (G-CSF) preparations are widely used for neutropenia.[1,2] Four G-CSF preparations have been marketed in Japan: filgrastim including three follow-on biologics, nartograstim, lenograstim, and pegfilgrastim. Among those, pegfilgrastim is only approved for prophylaxis of neutropenia caused by antineoplastic agents but not for neutropenia treatment for which the other G-CSF preparations are approved.[3]

Since the marketing of pegfilgrastim in November 2014, several spontaneous case reports indicating severe thrombocytopenia

in patients treated with pegfilgrastim have been accumulated.[4] Similar cases have also been recognized in patients treated with the other G-CSF preparations.[4] However, many reported cases were of patients with cancer and the observed thrombocytopenia could have been caused by antineoplastic agents but not G-CSF preparations. Therefore, the Pharmaceuticals and Medical Devices Agency (PMDA) decided to conduct a pharmacoepidemiologic study to investigate the association between G-CSF preparations marketed in Japan and thrombocytopenia in patients treated with antineoplastic agents.

This article describes the Medical Information Database NETwork (MID-NET®) study and PMDA's consideration on the risks of thrombocytopenia associated with G-CSF preparations in patients treated with antineoplastic agents in Japan.

METHODS
Database
Data from MID-NET®, a reliable and valuable database in Japan,[5,6] were used for analysis in this study, because MID-NET® stores electronic medical records, administrative claim data, and diagnosis procedure combination data of about 5.3 million patients (as of December 2020) in cooperation with 10 healthcare organizations, including 23 university hospitals or regional core hospitals. In this database, platelet count data, which are an appropriate indicator for thrombocytopenia are available for analysis. In addition, the outcome of this study (occurrence of thrombocytopenia after administration of G-CSF preparations during the treatment period with antineoplastic agents) can be obtained in the same hospital, even though MID-NET® can only follow-up a patient within a hospital.[5] The study period was from January 1, 2009, to September 30, 2018.

The utilization of MID-NET® for this study was approved on June 29, 2018, by the expert committee of MID-NET®.[7] Because this study was conducted as an official activity of PMDA under the Pharmaceuticals and Medical Devices Agency Law (Article 15–5–(c) and (f)),[8] it was not subject to review by institutional review boards.[9]

Study design
A nested case-control design was selected to account for many covariates just prior to the occurrence of thrombocytopenia, such as type of antineoplastic agent and its treatment length, commodity, and co-prescribed drugs.

Cohort
The cohort included patients who were prescribed any antineoplastic agent (see **Table S1** for the code list) in the month with the record of that cancer diagnosis coded (International Classification of Diseases 10th revision (ICD-10) code[10]: C00-C97, D00-09, D47-48), but excluded the following: (1) patients without medical records within 90 days before t_0 (first prescription date of any antineoplastic agents), (2) patients without medical records more than 30 days after the last prescription date of any antineoplastic agent, (3) patients diagnosed with myeloid leukemia (ICD-10 code: C92-93, D47) at any time during the entire data period, and (4) patients with a history of thrombocytopenia prior to t_0.

The follow-up period of this cohort was started at t_0 and ended at the earlier date according to the following: (1) the end date of the last treatment period with antineoplastic agents or (2) the date of the incident date of thrombocytopenia (refer to the case definition). The treatment period consisted of the prescription date with a 30-day gap and a 30-day grace period. Thus, two prescriptions for same drug(s) were recognized as a succeeded treatment if the later prescription date was within 30 days of the former prescription date.

Case and control definition
A case of thrombocytopenia was defined as a patient whose platelet counts were decreased to less than 50,000/mm^3 (Common Terminology Criteria for Adverse Events (CTCAE) version 4.0,[11] grade 3), a clinically important criterion indicating an occurrence of thrombocytopenia, during the treatment period of the antineoplastic agent. The index date of the case was the earliest date of occurrence of the thrombocytopenia in the follow-up period. For each case, controls (maximum 10) were selected from patients without thrombocytopenia during the treatment period with antineoplastic agent, who were matched with a case on the index date according to the following variables: sex, age (± 5 years), healthcare organizations, and the most recent antineoplastic prescription (by generic name) and the calendar date (± 180 days). The index date of control was chosen to be equal to the follow-up time to that of the case.

Exposure definition
Users and nonusers of G-CSF preparations were defined as the population who had prescriptions and did not have prescriptions of any G-CSF preparations in the time window defined by within 30 days before and on the index date, respectively. The patients with prescriptions of G-CSF preparations only at more than 30 days before the index date (out of the time window) were categorized as nonuser for analysis. To analyze the timing of G-CSF preparation use, users of G-CSF preparation were divided into 3 categories comprising the index date, 1–7 days before and 8–30 days before the index date. In the detailed analysis, users of G-CSF preparations were further divided into 1 day and 2–7 days before the index date, and subsequently every 7 days from the index date.

Statistical analysis
Patient background, including matching factors and the other relevant patient characteristics, such as cancer diagnosis based on ICD-10[10] in the same month as the index date and radiological therapy within the entire period before the index date, was tabulated. To evaluate the association between the use of G-CSF preparations and thrombocytopenia, conditional logistic regression analysis considering with matching factors was conducted to estimate crude ORs and adjusted ORs (aOR) with adjustment for the occurrence of radiological therapy. Similar analysis was conducted on each drug in the detailed analysis. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Sensitivity and additional analysis
The following analyses were conducted as a sensitivity analysis: (1) the criterion of a case with thrombocytopenia was tightened to less than 25,000/mm^3 (CTCAE version 4.0,[11] grade 4), and (2) the end of the follow-up period was shortened to 8 weeks or 12 weeks from t_0 in order to eliminate the effects of hematopoietic disorders that could develop from prolonged use of antineoplastic agents.

Furthermore, two additional analyses were performed to confirm the robustness of the results. One was on the study cohort excluding patients prescribed filgrastim, nartograstim, and lenograstim in order to focus on the investigation of the association between pegfilgrastim and thrombocytopenia. The second was on the study cohort without exclusion criterion (2), to include the patients who did not follow-up on hospital visits just after the start of antineoplastic agents in the analysis. In addition, descriptive analysis for examining the trend of decreased platelet counts before and after the initiation of G-CSF preparation use was also conducted in the subgroups comprising exposure to pegfilgrastim, and exposure to filgrastim, nartograstim, or lenograstim.

RESULTS
Cohort, case, and control
Of the 176,019 patients who were prescribed any antineoplastic agents, 33,124 patients were included in the study cohort after

applying the inclusion and exclusion criteria. A total of 733 cases and 5,592 controls were identified from the cohort (**Figure 1**).

Patient characteristics

Table 1 shows the characteristics of the patients in this study, with similar distributions in the matching variables between cases and controls. Cases and controls on nonmatching variables, such as cancer type distribution and incidence of radiological therapy were also similar. For example, "malignant neoplasms of digestive organs" (74.5% for cases vs. 78.9% for controls) and "malignant neoplasms of ill-defined, secondary and unspecified sites" (51.8% for cases vs. 41.5% for controls) were major types of cancer diagnosis for both cases and controls. The median days from t_0 to index date were slightly shorter in the cases, but the interquartile range overlapped between cases and controls.

Association between G-CSF preparations and thrombocytopenia

In comparison with nonusers of G-CSF preparations, aORs on thrombocytopenia of users of G-CSF preparations (including all G-CSF preparations) in the entire time window (31 days including the index date) significantly increased by 5.7 (95% confidence interval (CI): 4.3–7.5). The highest aOR was observed on the index date (18.1, 95% CI: 12.0–27.4) followed by 1–7 days before the index date (2.6, 95% CI: 1.7–4.2; **Table 2**).

Because a higher aOR was observed on the index date and 1–7 days before the index date, we conducted further detailed analyses focusing on the days closest to the index date and on each G-CSF preparation, as shown in **Figure 2**. Interestingly, aOR for pegfilgrastim significantly increased at 2–7 days before the index date (7.4, 95% CI: 2.0–28.1) and no cases with pegfilgrastim were actually found on the index date and 1 day before the index date (see **Table S2** for all analytical results up to 30 days before the index date). Similar results for pegfilgrastim were also observed in the sensitivity analyses and additional analyses, such as changing the criterion of platelet counts for thrombocytopenia (see **Table S3**), changing the follow-up period (see **Table S4-1**, **Table S4-2**), a different cohort excluding patients treated with filgrastim, nartograstim, and lenograstim (see **Table S5**) and a different cohort without exclusion criterion (2) (**Table S6**).

The increase in aOR for other G-CSF preparations except for pegfilgrastim were similar to those calculated for all G-CSF preparations combined. The highest aOR was observed on the index date for all three G-CSF preparations (filgrastim: 22.4, 95% CI: 13.1–38.4, lenograstim: 13.4, 95% CI: 6.0–30.2, and nartograstim: 13.4, 95% CI: 3.2–55.3). For filgrastim, a significantly increased aOR was also observed 1 day before the index date, as shown in **Figure 2**, and these effects were confirmed in the sensitivity and additional analyses (see **Table S3**, **Table S4-1**, **Table S4-2**, **Table S6**). Higher aORs on different days other than the index
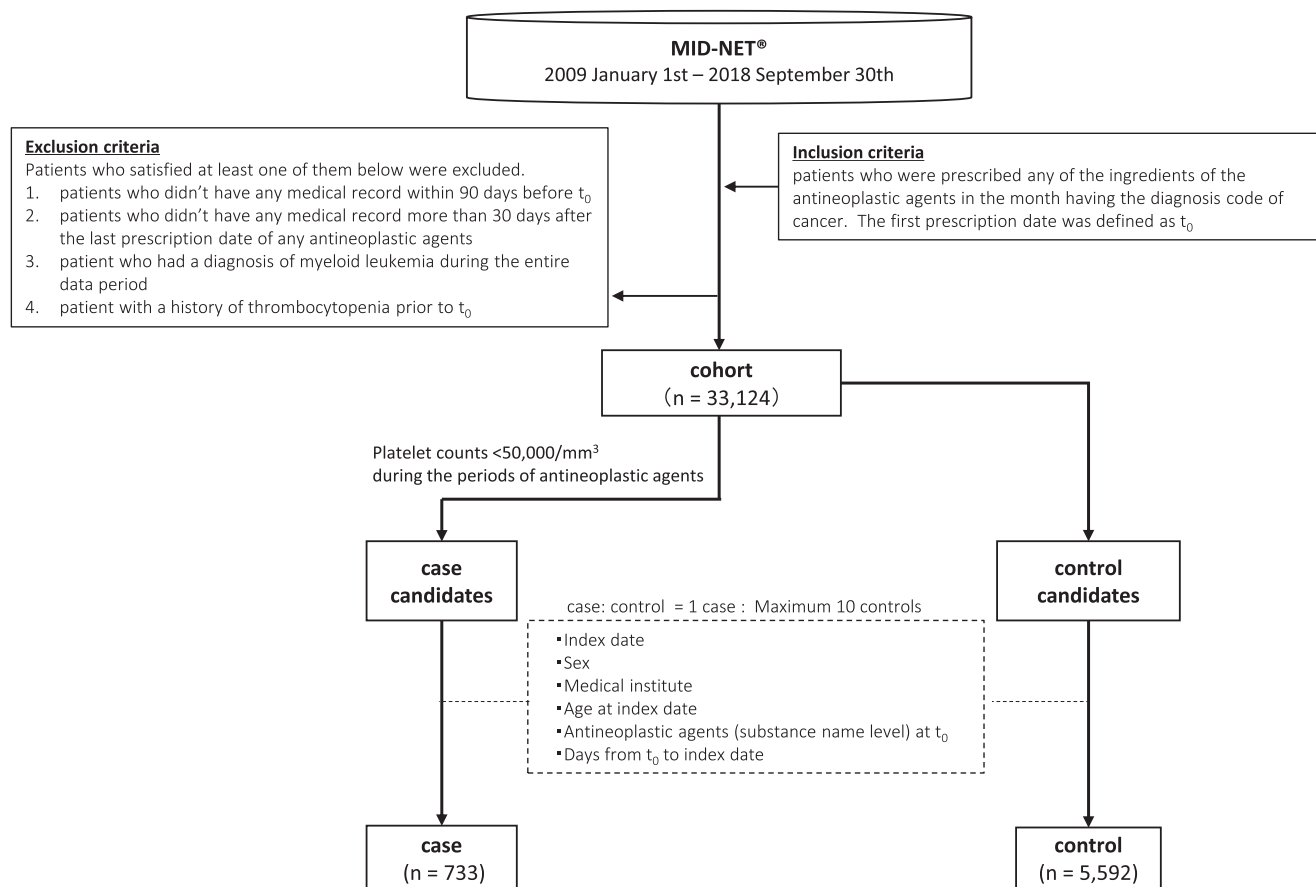

Figure 1 Study flow chart.

Table 1 Patient characteristics of cases and controls in this study

	Cases[c]	Controls[c]
	Number of patients (%)	Number of patients (%)
Total	733 (100.0%)	5,592 (100.0%)
Gender at index date[a]		
Female	230 (31.4%)	1,659 (29.7%)
Male	503 (68.6%)	3,933 (70.3%)
Age at index date[a]		
0–29	0 (0.0%)	0 (0.0%)
30–39	< 10 (< 1.4%)	21 (0.4%)
40–49	< 20 (< 2.7%)	104 (1.9%)
50–59	49 (6.7%)	323 (5.8%)
60–69	232 (31.7%)	1,751 (31.3%)
70–79	348 (47.5%)	2,725 (48.7%)
80–over	83 (11.3%)	668 (12.0%)
Median (interquartile)	72 (66–76)	72 (66–77)
Antineoplastic agents at index date (Top 10)[a]		
Gemcitabine hydrochloride	152 (20.7%)	1,120 (20.0%)
Tegafur, gimeracil, and oteracil potassium	111 (15.1%)	1,010 (18.1%)
Epirubicin hydrochloride	78 (10.6%)	724 (12.9%)
Carboplatin and paclitaxel	79 (10.8%)	603 (10.8%)
Miriplatin hydrate	19 (2.6%)	157 (2.8%)
Rituximab (genetic recombination)	24 (3.3%)	152 (2.7%)
Methotrexate	19 (2.6%)	144 (2.6%)
Cisplatin	24 (3.3%)	136 (2.4%)
Bicalutamide	13 (1.8%)	129 (2.3%)
Capecitabine and oxaliplatin	16 (2.2%)	118 (2.1%)
Days from the initiation of the most recent antineoplastic agents' therapy to the index date[a]		
Median (interquartile)	14 (8–30)	14 (7–28)
Minimum, maximum	0, 236	0, 236
Diagnosis for cancer (ICD-10) at t_0		
C00-97 malignant neoplasms		
C00-14 lip, oral cavity, and pharynx	32 (4.4%)	125 (2.2%)
C15-26 digestive organs	546 (74.5%)	4,414 (78.9%)
C30-39 respiratory and intrathoracic organs	84 (11.5%)	571 (10.2%)
C40-41 bone and articular cartilage	< 10 (< 1.4%)	10 (0.2%)
C43-44 melanoma and other malignant neoplasms of skin	< 10 (< 1.4%)	35 (0.6%)
C45-49 mesothelial and soft tissue	< 10 (< 1.4%)	43 (0.8%)
C50 breast	21 (2.9%)	110 (2.0%)
C51-58 female genital organs	100 (13.6%)	763 (13.6%)
C60-63 male genital organs	55 (7.5%)	460 (8.2%)
C64-68 urinary tract	169 (23.1%)	973 (17.4%)
C69-72 eye, brain, and other parts of the central nervous system	< 10 (< 1.4%)	< 10 (< 0.2%)
C73-75 thyroid and other endocrine glands	< 10 (< 1.4%)	36 (0.6%)
C76-80 ill-defined, other secondary and unspecified sites	380 (51.8%)	2,322 (41.5%)

(Continued)

Table 1 (Continued)

	Cases[c]	Controls[c]
	Number of patients (%)	Number of patients (%)
C81-96 lymphoid, hematopoietic. and related tissue[b]	81 (11.1%)	412 (7.4%)
C97 independent (primary) multiple sites	0 (0.0%)	0 (0.0%)
D00-09 *in situ* neoplasms	< 10 (< 1.4%)	19 (0.3%)
D37-48 neoplasms of uncertain or unknown behavior[b]	0 (0.0%)	0 (0.0%)
Radiological therapy before the index date		
Experienced	128 (17.4%)	652 (11.7%)
Nonexperienced	605 (82.5%)	4,940 (88.3%)
Days from t_0 to the index date		
Median (interquartile range)	68 (14–245)	92 (14–355)
Minimum, maximum	0, 3236	0, 3273

ICD-10, International Classification of Diseases 10th Revision; MID-NET®, Medical Information Database NETwork.
[a]Matching factors. [b]Patients diagnosed with myeloid leukemia (ICD-10 code: C92-93, D47) at any time during the entire data period were excluded from the cohort. [c]When a value was < 10, it was shown as an aggregated value based on the MID-NET® publication rule.

Table 2 Association between G-CSF preparations and thrombocytopenia

	Cases	Controls	Crude odds ratio[a]	Adjusted odds ratio[a,b]
Exposure category	*n* = 733	*n* = 5592	(95% CI)	(95% CI)
Non G-CSF prescription	586	5254	1 (reference)	1 (reference)
Any G-CSF preparation	147	338	5.9 (4.5–7.7)	5.7 (4.3–7.5)
Exposure timing of any G-CSF preparation				
On the index date	100	91	18.7 (12.4–28.3)	18.1 (12.0–27.4)
1–7 days before the index date	32	155	2.7 (1.7–4.3)	2.6 (1.7–4.2)
8–30 days before the index date	15	92	1.7 (0.9–3.1)	1.7 (0.9–3.1)

It should be noted that in cases where the timings of G-CSF preparation prescription and thrombocytopenia were obscure, these timings were recorded as the index date (same day), because an exact time was not available in MID-NET®. Thus, cases on the index date may include a patient whose platelet counts were decreased before the prescription of G-CSF preparations.
CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; MID-NET®, Medical Information Database NETwork.
[a]Estimated by a conditional logistic regression model. [b]Estimated by a conditional logistic regression model with adjustment of radiological therapy.

date for lenograstim were inconsistent with the results in the sensitivity and additional analyses (see **Table S3**, **Table S4**-1, **Table S4**-2, **Table S6**).

Furthermore, evaluation of the trend of the average of platelet counts before and after the initiation of G-CSF preparations, showed that the platelet count before and on the start date of pegfilgrastim in the cases was sufficiently higher than the criterion for thrombocytopenia, whereas in cases with the other G-CSF preparations, a substantial decrease in the platelet count approaching the criterion even a few days before and on the start date of filgrastim, lenograstim, or nartograstim (see **Figure S1**-1, **Figure S1**-2).

DISCUSSION

In this study, a significant increase in aOR on thrombocytopenia was observed when pegfilgrastim was prescribed 2–7 days before the index date as compared with nonusers of G-CSF preparations. This effect of pegfilgrastim was consistent with the results from the sensitivity/additional analyses. In the descriptive trend analysis on the average of platelet counts before and after the initiation of G-CSF preparation, sufficiently higher platelet counts before

and on the start date of pegfilgrastim in cases also support the evidence that the observed thrombocytopenia is due to initiation of pegfilgrastim treatment and are not effects of antineoplastic agents. These results indicate that the thrombocytopenia in the patients treated with antineoplastic agents is associated with the prescription of pegfilgrastim.

In contrast, increased aOR by the other G-CSF preparations (filgrastim, nartograstim, and lenograstim) was mainly observed on the index date. This high aOR on the index date could be explained by a reverse causality on the timing between the onset of thrombocytopenia and the prescription of these G-CSF preparations, because an exact time for the onset of these events was not available in MID-NET®. Specifically, G-CSF preparations, except pegfilgrastim, were usually prescribed for neutropenia treatment (recovery of neutrophil counts) and due to their limited indication, a slight decrease in platelet counts might have already occurred before the initiation of G-CSF preparations. In the patients exposed to the filgrastim, nartograstim, or lenograstim, a substantial decrease in platelet counts was observed in cases even a few days before the initiation of the G-CSF preparation as compared with

	time window	cases *	control *	crude odds ratio †	95% CI		adjusted odds ratio ‡	95% CI	
non G-CSF exposed	Entire period (31 days)	586	5254	1	-	-	1	-	-
pegfilgrastim	on the Index Date	0	0	-	-	-	-	-	-
	1 day before the Index Date	0	<10	-	-	-	-	-	-
	2-7 days before the Index Date	<10	38	7.7	2.0 -	29.1	7.4	2.0 -	28.1
	8-14 days before the Index Date	<10	<20	3.2	0.8 -	12.6	3.1	0.8 -	12.4
filgrastim	on the Index Date	71	57	23.2	13.6 -	39.7	22.4	13.1 -	38.4
	1 day before the Index Date	<10	12	6.1	2.1 -	17.9	6.1	2.1 -	18.1
	2-7 days before the Index Date	<10	69	1.3	0.6 -	3.1	1.2	0.5 -	2.9
	8-14 days before the Index Date	<10	27	0.9	0.2 -	4.1	0.8	0.2 -	3.9
lenograstim	on the Index Date	<30	24	14.0	6.2 -	31.4	13.4	6.0 -	30.2
	1 day before the Index Date	<10	<10	10.8	1.7 -	69.3	10.7	1.7 -	67.5
	2-7 days before the Index Date	<10	12	3.7	1.1 -	12.5	3.7	1.1 -	12.4
	8-14 days before the Index Date	0	<10	-	-	-	-	-	-
nartograstim	on the Index Date	<10	10	13.3	3.2 -	55.0	13.4	3.2 -	55.3
	1 day before the Index Date	<10	<10	2.6	0.3 -	25.2	2.3	0.2 -	23.0
	2-7 days before the Index Date	<10	10	0.6	0.1 -	5.4	0.6	0.1 -	5.6
	8-14 days before the Index Date	<10	<10	1.6	0.3 -	8.1	1.6	0.3 -	7.9
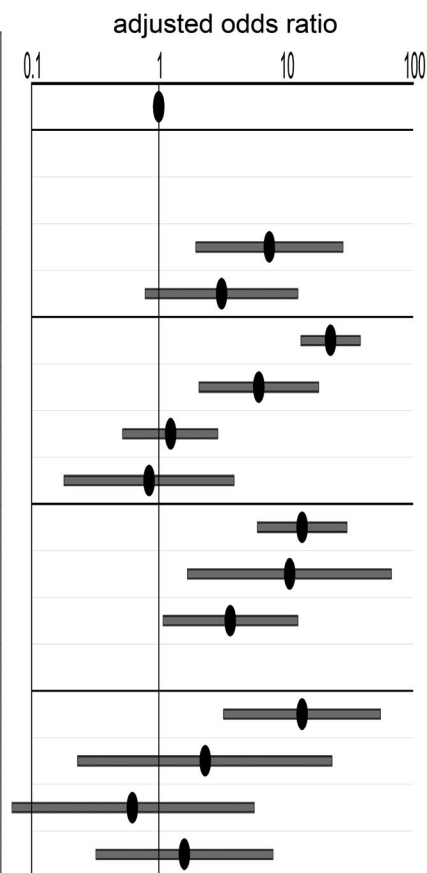
Figure 2 Forest plot of adjusted odds ratios showing the association between each G-CSF preparation and thrombocytopenia using detailed time windows. *When a value was less than 10, it was shown as an aggregated value based on the MID-NET® publication rule. †Estimated by a conditional logistic regression model. ‡Estimated by a conditional logistic regression model with adjustment of radiological therapy. It should be noted that in cases where the timings of G-CSF preparation prescription and thrombocytopenia were obscure, those timings were recorded as the index date (same day), because an exact time was not available in MID-NET®. Thus, cases on the index date may include a patient whose platelet counts were decreased before the prescription of G-CSF preparations. CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; MID-NET®, Medical Information Database NETwork.

controls (see **Figure S1**-1, **Figure S1**-2), which supports this consideration. The higher aOR 1 day before and on the index date for filgrastim may be also explained by this. Such phenomena were not observed for pegfilgrastim, because pegfilgrastim was prophylactically prescribed only for suppression of neutropenia caused by antineoplastic agents. In fact, no cases 1 day before and on the index date were identified in patients treated with pegfilgrastim. These results show no clear associations between thrombocytopenia and the G-CSF preparations except for pegfilgrastim. Further studies would be necessary to clarify these relationships.

The strength of this study was on the utilization of longitudinal laboratory test results of platelet counts as an outcome of thrombocytopenia from MID-NET®, a reliable database.[5] However, as a limitation, other potential confounders, such as performance status, dosage of antineoplastic agents, and bone marrow infiltration, could not be taken into consideration due to the characteristics of MID-NET®, although no major differences on cumulative doses of antineoplastic agents were confirmed between cases and controls (data not shown).

The PMDA conducted a safety assessment on the risk of thrombocytopenia in association with G-CSF preparations based on case reports and related literature as well as the results from this study. In March 2020, the PMDA announced a revision of the package insert of pegfilgrastim to inform G-CSF-induced thrombocytopenia.[12]

CONCLUSION

A significantly increased risk of thrombocytopenia associated with pegfilgrastim was identified. This finding was the key evidence for the PMDA regulatory safety action of revising the label (prescribing information) of pegfilgrastim. More attention on thrombocytopenia may be necessary during treatment with pegfilgrastim.

AUTHOR CONTRIBUTIONS

C.I., K.K., Y.U., Y.K., N.K., Y.O., and T.I. wrote the manuscript. C.I., K.K., Y.U., Y.K., N.K., Y.O., and T.I. designed the research. K.K., C.I., and Y.K. performed the research. K.K. and T.A. analyzed the data.

PAST PRESENTATION ON THIS RESEARCH

A portion of this article was included in the official Pharmaceuticals and Medical Devices Agency (PMDA) report, which is available at the PMDA website (https://www.pmda.go.jp/files/000234446.pdf).

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