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Summary of MID-NET® study: No. 2018-002

March 31, 2020

Study title

A pharmacoepidemiological study on the association between G-CSF preparations and decreased platelet counts

Products investigated

Nartograstim (genetical recombination), filgrastim (genetical recombination) and the follow-on biologics, pegfilgrastim (genetical recombination), lenograstim (genetical recombination)

Background

- Several cases involving thrombocytopenia in patients treated with G-CSF[1] preparations have been reported.
- Since G-CSF preparations may be administered in patients on cancer chemotherapy, thrombocytopenia reported could be an effect of antineoplastic agents. This possibility poses a limitation to the assessment of the association between individual G-CSF preparations and thrombocytopenia solely based on the information from individual case reports.

[1] Granulocyte-colony stimulating factor

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Purpose of the study

To compare in patients receiving antineoplastic agents the onset status of decreased platelet counts between the presence and absence of the prescription of G-CSF preparations and investigate the association between G-CSF preparations and decreased platelet counts.

Reason to select MID-NET® for the study

Reason to select: To perform evaluation with laboratory test results as an index.

Data from 21 hospitals at 9 healthcare organizations cooperating with MID-NET® whose data were available throughout the target data period.

Data period: January 1, 2009 to September 30, 2018

Outline of method

Based on the nested case-control design, to evaluate the association between G-CSF preparations and decreased platelet counts with a focus on the development or no development of decreased platelet counts in patients receiving an identical antineoplastic agent(s).

Outline of results

- **Study population**

- Of the 176 019 patients who were prescribed any of the 177 ingredients of the antineoplastic agents investigated, 33 124 patients were included in the study population after excluding patients with a history of decreased platelet counts and patients with a history or complication of myeloid leukemia prior to the start of antineoplastic prescription.
- A total of 733 patients (cases) who developed decreased platelet counts[2] while prescribed antineoplastic agents were identified from the 33 124 patients, as well as 5 592 patients (controls) originated 180 days before and after the onset date of decreased platelet counts as their matches in the following variables:
  < Matching variables > Sex, age (± 5 years), healthcare organizations, type of the most recent antineoplastic prescription initiated (by generic name), and number of days from

[2] grade 3 or higher cases (platelet counts <50 000 mm^3) according to the Common Terminology Criteria for Adverse Event version 4.0 (CTCAE v4.0)

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the day antineoplastic prescription was initiated.

- **Patient background**
  - **Matching variables:** In cases (n = 733) and controls (n = 5 592), males accounted for 68.6% and 70.3%, respectively, and the median age (interquartile range) was 72 years (66-76) and 72 years (66-77), respectively. The median number of days (interquartile range) from the day the most recent antineoplastic prescription started to the onset date of decreased platelet counts or the corresponding index date was 14 days (8-30) and 14 days (7-28), respectively. Major antineoplastic agents most recently prescribed on the onset date of decreased platelet counts or the index date include “gemcitabine hydrochloride” (20.7% for cases, 20.0% for controls), “tegafur/gimeracil/oteracil potassium" (15.1%, 18.1%), and "paclitaxel and carboplatin" (10.8%, 10.8%), and “epirubicin hydrochloride” (10.6%, 13.0%).
  - Other than matching variables: The major cancer diseases by ICD-10[3] (2013 version) were “malignant neoplasms of digestive organs” (74.5% for cases, 78.9% for controls) and “malignant neoplasms of ill-defined, secondary and unspecified sites” (51.8%, 41.5%). The median number of days (interquartile range) from the start date of the earliest antineoplastic prescription to the onset date of decreased platelet counts or the corresponding index date was 68 days (14-245) for cases and 92 days (14-355) for controls.

[3] International Statistical Classification of Diseases and Related Health Problems (Ver. 10)

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■ **Association between G-CSF preparations and decreased platelet counts**

- Regarding decreased platelet counts following prescription of pegfilgrastim (genetical recombination) (hereinafter “pegfilgrastim”), the relative risk (adjusted odds ratio) of decreased platelet counts was statistically significantly elevated when pegfilgrastim was prescribed 2 to 7 days before decreased platelet counts developed compared to no prescriptions of G-CSF preparations (see the Table below). A similar trend was observed when analysis was limited to 8-week and 12-week observation periods from the initial antineoplastic prescription in order to eliminate the effects of hematopoietic disorders that could develop from prolonged use of antineoplastic agents and when the criterion for decreased platelet counts was changed to lower than 25 000/mm^3 (CTCAE v 4.0 Grade 4). An analysis was performed on a study population restricted to patients prescribed pegfilgrastim with similarly matched controls and excluding those patients prescribed G-CSF preparations excluding pegfilgrastim in order to investigate the association between pegfilgrastim and decreased platelet counts complementally. As a result, although in a study population with a reduced number of cases, a similar trend to the original analysis was observed with elevated point estimation values for the relative risk of decreased platelet counts in patients who were prescribed pegfilgrastim 2 to 7 days prior to decreased platelet counts compared to patients with no prescription of G-CSF preparations.
- In patients prescribed pegfilgrastim, the median number of days from the day the most recent antineoplastic prescription started to the day pegfilgrastim was prescribed (interquartile range) was 6 days (4-21) for cases (n =14) and 6 days (6-23) for controls (n =60).
- In all the case patients prescribed pegfilgrastim (n =14), the platelet count was 60 000/mm^3 or higher on the day pegfilgrastim was prescribed, and all the case patients experienced a platelet count decrease to less than 50 000/mm^3 within 30 days from the next day. In more than half of these patients, the platelet counts decreased to lower than 50 000/mm^3 within 14 days from the day after the pegfilgrastim prescription.

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- For G-CSF preparations excluding pegfilgrastim, patients were often prescribed preparations on the day decreased platelet counts occurred, and the relative risk of the event on the day of prescription significantly elevated compared to that of the patients with no prescription of G-CSF preparations. The temporal relationship on the day of prescription between the onset timing of decreased platelet counts and the prescription of G-CSF preparations is unknown. The relative risk of decreased platelet counts was also statistically significantly elevated in patients prescribed G-CSF preparations the day before the event. However, in many patients, platelet count tended to decrease already before the day G-CSF preparations were prescribed. An elevation in the relative risk of decreased platelet counts was observed in some time points when G-CSF preparations were prescribed 2 to 30 days prior to decreased platelet counts, when the observation was limited to 12-week and 16-week periods from the initial antineoplastic prescription, when the criterion for platelet counts was changed, or when analysis was performed to a study population restricted to patients prescribed G-CSF preparations excluding pegfilgrastim with similarly matched controls to the original analysis study population. No consistent trends however, were revealed in these elevations.

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■ Discussion based on the results

- A statistically significant elevation in the relative risk of decreased platelet counts was observed regarding pegfilgrastim when the drug was prescribed 2 to 7 days before the event and similar trends were suggested in sensitivity analyses.
- An association between the preparations and decreased platelet counts could not be determined for G-CSF preparations excluding pegfilgrastim because effects by antineoplastic agents could not be ruled out.
- It should be noted that there are some limitations such as other potential confounders including performance status and applied dosage amount of antineoplastic agents which may affect the results.

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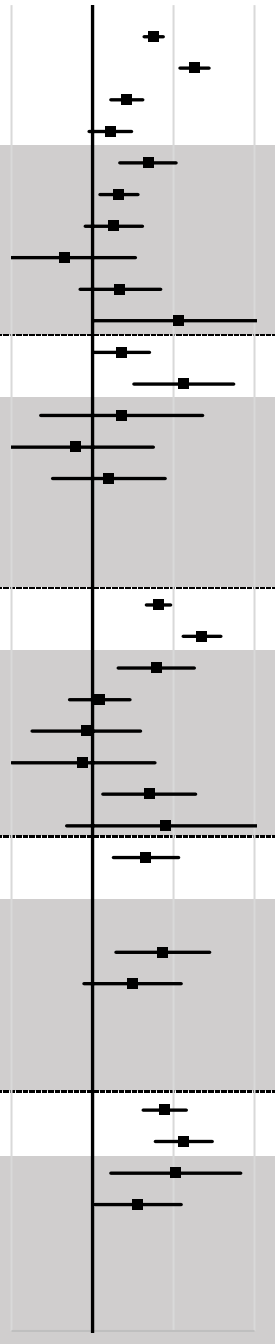
➢ Table of G-CSF preparations and decreased platelet counts

Exposure category	Cases n =733	Controls n = 5,592	Crude odds ratio ‡ (95% CI)	Adjusted odds ratio ¶ (95% CI)
No G-CSF prescription	586	5,254	1 (reference)	1 (reference)
Any G-CSF prescribed	147	338	5.89 (4.48-7.74)	5.68 (4.32-7.47)
On the Index date (ID) † ∗	100	91	18.7 (12.4-28.3)	18.1 (12.0-27.4)
1-7 days before ID	32	155	2.73 (1.73-4.31)	2.64 (1.68-4.17)
8-30 days before ID	15	92	1.70 (0.93-3.12)	1.67 (0.91-3.05)
The day before ID	10	26	4.95 (2.23-11.0)	4.86 (2.18-10.8)
2-7 days before ID	22	129	2.21 (1.29-3.77)	2.12 (1.24-3.63)
8-14 days before ID	<10	50	1.90 (0.84-4.30)	1.83 (0.81-4.13)
15-21 days before ID	<10	25	0.45 (0.06-3.35)	0.45 (0.06-3.39)
22-28 days before ID	<10	<20	2.31 (0.74-7.28)	2.20 (0.70-6.93)
29-30 days before ID	<10	<10	11.0 (0.97-123.1)	11.7 (1.03-132.2)
Nartograstim prescribed	10	39	2.28 (1.04-4.98)	2.31 (1.06-5.04)
On the ID †∗	<10	10	13.3 (3.20-55.0)	13.4 (3.23-55.3)
The day before ID	<10	<10	2.55 (0.26-25.2)	2.32 (0.23-23.0)
2-7 days before ID	<10	10	0.60 (0.07-5.37)	0.62 (0.07-5.64)
8-14 days before ID	<10	<10	1.62 (0.32-8.07)	1.59 (0.32-7.92)
15-21 days before ID	0	<10	incalculable	incalculable
22-28 days before ID	0	<10	incalculable	incalculable
29-30 days before ID	0	0	incalculable	incalculable
Filgrastim prescribed	93	190	6.81 (4.82-9.63)	6.53 (4.62-9.25)
On the ID †∗	71	57	23.2 (13.6-39.7)	22.4 (13.1-38.4)
The day before ID	<10	12	6.06 (2.05-17.9)	6.12 (2.07-18.1)
2-7 days before ID	<10	69	1.32 (0.56-3.10)	1.24 (0.52-2.91)
8-14 days before ID	<10	27	0.88 (0.19-4.08)	0.84 (0.18-3.91)
15-21 days before ID	<10	<20	0.77 (0.10-6.00)	0.75 (0.10-5.89)
22-28 days before ID	<10	<10	5.56 (1.50-20.6)	5.01 (1.34-18.7)
29-30 days before ID	<10	<10	7.56 (0.45-126.1)	7.98 (0.48-132.5)
Pegfilgrastim prescribed	14	60	4.69 (1.85-11.9)	4.58 (1.81-11.6)
On the ID †∗	0	0	incalculable	incalculable
The day before ID	0	<10	incalculable	incalculable
2-7 days before ID	<10	38	7.68 (2.02-29.1)	7.40 (1.95-28.1)
8-14 days before ID	<10	<20	3.15 (0.79-12.6)	3.12 (0.78-12.4)
15-21 days before ID	0	<10	incalculable	incalculable
22-28 days before ID	0	<10	incalculable	incalculable
29-30 days before ID	<10	0	incalculable	incalculable
Lenograstim prescribed	30	49	8.05 (4.36-14.9)	7.79 (4.22-14.4)
On the ID †∗	<30	24	14.0 (6.22-31.4)	13.4 (5.95-30.2)
The day before ID	<10	<10	10.8 (1.69-69.3)	10.7 (1.68-67.5)
2-7 days before ID	<10	12	3.70 (1.09-12.5)	3.65 (1.08-12.4)
8-14 days before ID	0	<10	incalculable	incalculable
15-21 days before ID	0	<10	incalculable	incalculable
22-28 days before ID	0	<10	incalculable	incalculable
29-30 days before ID	0	0	incalculable	incalculable



†: The day decreased platelet counts developed or the corresponding index date
‡: Estimated by a conditional logistic regression model
¶: Estimated by a conditional logistic regression model in which the presence or absence of radiological therapy was considered.
∗: The temporal relationship on the index date between the onset timing of decreased platelet counts and the prescription of G-CSF preparations is unknown.

Note: Aggregate values of less than 10 are masked to prevent identification of patients according to the MID-NET publication criteria.

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