Incidence of gastrointestinal perforation associated with bevacizumab in combination with neoadjuvant chemotherapy as first-line treatment of advanced ovarian, fallopian tube, or peritoneal cancer: analysis of a Japanese healthcare claims database

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ABSTRACT

Objective: To assess the incidence of bevacizumab-associated gastrointestinal (GI) perforation during first-line treatment of patients with ovarian, fallopian tube, or peritoneal cancer receiving neoadjuvant chemotherapy (NAC) in Japanese real-world clinical practice.

Methods: A retrospective study was conducted using a healthcare claims database owned by Medical Data Vision Co., Ltd. (study period, 2008–2020). Patients who initiated first-line treatment of ovarian, fallopian tube, or peritoneal cancer were identified and divided into NAC and primary debulking surgery (PDS) groups. The incidence of bevacizumab-associated GI perforation was compared within the NAC group and between the groups.

Results: Paclitaxel + carboplatin (TC) was most commonly used as first-line treatment (39.5% and 59.6% in the NAC and PDS groups, respectively). TC + bevacizumab was used in 9.3% and 11.6% of patients in the NAC and PDS groups, respectively. In the NAC group receiving TC, the proportion of patients with risk factors for GI perforation was lower among patients with versus without concomitant bevacizumab. The incidence of GI perforation in the NAC group was 0.38% (1/266 patients) in patients receiving TC + bevacizumab and 0.18% (2/1,131 patients) in patients receiving TC without bevacizumab (risk ratio=2.13; 95% confidence interval [CI]=0.19 to 23.36; risk difference=0.20; 95% CI=−0.58 to 0.97). None of the 319 patients in the PDS group receiving TC + bevacizumab had GI perforation.
INTRODUCTION

Ovarian cancer ranks as the eighth most common cancer and cause of cancer deaths in women worldwide [1]. In Japan, the projected number of ovarian cancer cases and deaths as of 2021 is 13,100 and 4,700, respectively [2]. The prognosis of advanced ovarian cancer (International Federation of Gynecology and Obstetrics stage III or IV) is poor; in Japan, the 5-year survival rates for stage III and IV ovarian cancer treated in 2013 were reported to be 49.2% and 33.2%, respectively [3]. The standard of care for first-line treatment of ovarian cancer is cytoreductive surgery and combination chemotherapy with platinum-containing drugs and taxane-based agents. Besides primary debulking surgery (PDS) with adjuvant chemotherapy [4,5], neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) is recommended in patients not eligible for optimal cytoreduction [4,5] or those who are elderly, are frail, or have poor performance status or comorbidities [4]. In Japan, the proportion of patients treated with NAC for ovarian cancer is increasing annually and reached 20.7% in 2018; however, the 5-year survival rate of NAC-treated patients was low at 44.8% as of 2013 [3]. Bevacizumab, an anti–vascular endothelial growth factor antibody, is recommended in the clinical guidelines for ovarian, fallopian tube, or peritoneal cancer [4,5], owing to its efficacy demonstrated in combination with NAC in clinical trials [6-8].

The safety of NAC containing bevacizumab followed by IDS for advanced ovarian cancer has been reported in several clinical trials and cohort studies. In the open-label, randomized, noncomparative, phase 2 ANTHALYA trial, no gastrointestinal (GI) perforation was observed as a postoperative complication in 58 patients receiving NAC containing bevacizumab [6]. In GEICO 1205, a randomized, open-label, phase 2 trial for newly diagnosed stage III/IV ovarian cancer, NAC with bevacizumab (administered to 35 patients) was not associated with an increased incidence of grade ≥3 adverse events (AEs) [7]. In a subgroup analysis of the MITO-16A-MaNGO OV2A phase 4 trial, surgical complications such as wound dehiscence (2 [2.7%] patients), wound healing delay (2 [2.7%]), and anastomotic dehiscence (1 [1.3%]) were reported in 74 patients who received NAC containing bevacizumab before IDS, but no perioperative deaths were reported [8]. Similarly, favorable safety profiles of NAC containing bevacizumab before IDS have been reported in Japanese patient populations [9,10], although the sample size was small. However, large-scale data in real-world clinical practice regarding AEs associated with bevacizumab treatment, such as GI perforation, thromboembolism, hypertension, GI bleeding, and proteinuria [11], remain insufficient. Particularly, GI perforation is a serious complication that requires urgent medical intervention and can have a significant impact on patient outcomes. Therefore, understanding the risk of GI perforation in patients treated with NAC containing bevacizumab is crucial for clinical practice in Japan.
perforations associated with perioperative bevacizumab use should be explored further as these events are severe AEs occurring more frequently in patients with ovarian cancer versus those with other solid tumors [12,13], owing to several factors, including tumor necrosis in the bowel serosa [14].

We conducted a retrospective cohort study to assess the incidence rate of GI perforation due to NAC containing bevacizumab in patients with ovarian, fallopian tube, or peritoneal cancer (hereafter, ovarian cancer) in Japanese real-world clinical practice. We also investigated the real-world treatment pattern of ovarian cancer in Japan.

MATERIALS AND METHODS

1. Study overview
This retrospective cohort study (University Hospital Medical Information Network identifier, UMIN000041175) was conducted using patient data extracted from a Japanese healthcare claims database. Among patients diagnosed with ovarian, fallopian tube, or peritoneal cancer (without multiple cancer diagnosis) between April 1, 2008, and January 29, 2020, those receiving first-line treatment were identified and classified into NAC and PDS groups. The observation period was set to ≥7 months. Patients whose first-line treatment was initiated between November 22, 2013, (bevacizumab approval date in Japan) and June 30, 2019, in each group were subjected to a treatment pattern analysis. Furthermore, the incidence rates of AEs, including those of GI perforation, were assessed in patients whose first-line treatment was paclitaxel + carboplatin (TC) or TC + bevacizumab. The primary outcome was comparison of the incidence rate of GI perforation during the first-line treatment period between patients with and without bevacizumab use in the NAC group. In addition, an interrupted time series analysis was performed for the entire observation period to assess the incidence of GI perforation before and after the approval of bevacizumab in Japan.

2. Study design and data source
This study used a healthcare claims database owned by Medical Data Vision Co., Ltd. (Tokyo, Japan), the largest database in Japan that includes medical information of up to 30 million individuals obtained from up to 400 Japanese acute care hospitals employing the Diagnosis Procedure Combination system [15]. This study has been performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Non-Profit Organization MINS Ethics Committee (approval date, May 27, 2020; approval number, 200214). Informed consent was not applicable because this study used deidentified patient data and did not involve any personally identifiable information.

3. Patient definition
From the database, data for women with a diagnosis of ovarian cancer (International Classification of Diseases, 10th Revision [ICD-10] code, C56), fallopian tube cancer (C570), or peritoneal cancer (C482) between April 1, 2008, and January 29, 2020, were extracted (data cutoff date, March 31, 2020; Table S1). Among these patients, those with a suspected (post-treatment) outpatient follow-up or recurrence of ovarian cancer (e.g., diagnosis of ovarian cancer without medical practice records and diagnosis of recurrent ovarian cancer) were excluded from the study. Furthermore, those with a diagnosis of cancers other than ovarian, fallopian tube, or peritoneal cancer before the date of the first diagnosis of ovarian cancer were excluded.
Patients receiving first-line treatment were allocated to the NAC group (patients who had not undergone debulking surgery [defined as Japanese medical practice category K889-00; Japanese medical practice code, 150220710] within 90 days before chemotherapy initiation) and PDS group (patients who had undergone debulking surgery). Among the NAC and PDS groups, in view of the approval date of bevacizumab for ovarian cancer and the observation period of this study, patients whose first-line treatment initiation did not fall between November 22, 2013, and June 30, 2019, were excluded, and patients receiving TC or TC + bevacizumab as first-line treatment were subjected to the analysis of AE incidence.

4. Definitions of AEs and treatment regimens

AEs were defined using the ICD-10 codes and Japanese medical practice categories. GI perforation was defined as a combination of diagnosis of perforation or peritonitis, computed tomography performed within 7 days of diagnosis, and medical practice pertaining to surgery for GI perforation performed within 7 days of diagnosis (Table S2), which corresponds to grade ≥3 (invasive intervention indicated) events. A preplanned medical expert review was performed for all patients meeting the above definitions to confirm the suitability of the predefined definitions of GI perforation. Following this review, patients diagnosed with multiple cancers between the diagnosis of ovarian cancer and the end of treatment for first ovarian cancer recurrence were excluded, and no changes were applied to the definition of GI perforation. AEs other than GI perforation were defined by combining a disease diagnosis and imaging tests/cardiography pertaining to each diagnosis performed within 7 days of diagnosis (Table S3). Regimens generally recommended for ovarian cancer (Table S4) were analyzed as treatment regimens of this study; TC regimens in which paclitaxel had been prescribed in a ≤14-day interval were regarded as dose-dense TC (ddTC). A change from the basic regimen was deemed as a therapy for recurrence. In addition, repetition of the same regimen with a prescription interval of ≥3 months was regarded as a therapy for recurrence. When bevacizumab, olaparib, or bevacizumab + olaparib had been continued as maintenance therapy for the basic regimen, it was regarded as continuation of the same basic regimen.

5. Outcomes

The primary outcome was comparison of the incidence rate of GI perforation during the first-line treatment period between the NAC group receiving TC with bevacizumab (hereafter, NAC TC + Bev group) and the NAC group receiving TC (hereafter, NAC TC group). Key secondary outcomes included comparison of the incidence rate of GI perforation during the first-line treatment period between the NAC TC + Bev group and PDS group receiving TC with bevacizumab (hereafter, PDS TC + Bev group), incidence rate of AEs other than GI perforation (fistula, embolism and thrombosis of arteries or veins, intracranial hemorrhage, GI ulcer and bleeding, and interstitial pneumonia) during the first-line treatment period, treatment patterns for ovarian cancer (first-, second-, and third-line treatments), and time to first subsequent therapy (TFST). Preplanned exploratory outcomes included an interrupted time series analysis for the incidence rate of GI perforation in patients with advanced ovarian cancer (irrespective of bevacizumab use) before and after the approval of bevacizumab for ovarian cancer in Japan and the annual trend in the treatment of ovarian cancer (2013–2019).

To confirm the appropriateness of the definition of GI perforation used in the current study, we performed a post hoc sensitivity analysis by using an expanded definition of GI perforation. Additional ICD-10 codes pertaining to perforation or peritonitis and medical practice categories pertaining to GI surgery (e.g., colectomy/hemicolectomy, ruptured
intestinal suture, and small bowel resection) were added to the original definition of GI perforation. Moreover, the criterion “medical practice performed within 7 days after the diagnosis” was removed from the expanded definition (Table S5). The occurrence of GI perforation was confirmed by medical expert review.

6. Statistical analyses

The sample size was defined based on the feasibility of the study, in view of the number of cases of advanced ovarian cancer with GI perforation available in the healthcare claims database. No statistical hypothesis testing was performed, and no significance levels or statistical power was set.

Distribution of and change in the first-, second-, and third-line treatment were assessed using the Sankey diagram. Median TFST and its 95% confidence interval (CI) in the NAC group (in patients with and without bevacizumab use) were estimated using a Kaplan-Meier analysis. The incidence rate of GI perforation was compared between the groups by calculating the risk difference and risk ratio along with their 95% CIs. In addition, as a sensitivity analysis, the risk difference and risk ratio, along with their 95% CIs, were estimated based on the augmented inverse propensity weighted (AIPW) estimator adjusted by covariates (age, history of intestinal obstruction, history of fistula, history of GI perforation, and history of intra-abdominal abscess). These covariates were selected from potential confounding factors in view of their clinical importance. The incidence rate of GI perforation before and after the approval of bevacizumab for ovarian cancer in Japan was assessed using a segmented Poisson regression model for an interrupted time series analysis. The annual trend in first-line treatment of ovarian cancer in the NAC and PDS groups (2013–2019) was evaluated using descriptive statistics.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

1. Patient disposition

Among 29,789 patients with ovarian, fallopian tube, or peritoneal cancer in the healthcare claims database, 7,839 (NAC, 4,182; PDS, 3,657) were identified as those receiving first-line treatment. After excluding 1,318 and 897 patients in the NAC and PDS groups, respectively, whose first-line treatment initiation was beyond the prespecified period, 2,864 patients in the NAC group and 2,760 patients in the PDS group were subjected to treatment pattern analysis. Among these, 1,397 patients in the NAC group and 1964 patients in the PDS group received TC or TC + bevacizumab as first-line treatment and were subjected to the analysis of AE incidence rates (Fig. 1).

2. Treatment patterns for ovarian, fallopian tube, or peritoneal cancer and TFST

As first-line treatment (Fig. 2A), TC was most commonly used in both groups (NAC, 39.5%; PDS, 59.6%), followed by ddTC (NAC, 18.5%; PDS, 18.0%). TC + bevacizumab was used by 9.3% of patients in the NAC group and 11.6% in the PDS group. Of the 2,008 patients who received first-line TC, TC + bevacizumab, or ddTC in the NAC group, 59.9% and 42.2% received second- and third-line treatment, respectively (Fig. 2B), whereas of the 2,468 patients who received first-line TC, TC + bevacizumab, or ddTC in the PDS group, 35.5% and 22.7% received second- and third-line treatment, respectively (Fig. 2C). In the NAC
Patients with ovarian, fallopian tube, or peritoneal cancer
Patients for interrupted time series analysis n=29,789

Excluded
No prescription of antineoplastic agents n=21,950
after the date of the first diagnosis*
First ovarian, fallopian tube, or peritoneal cancer n=19,932
diagnosis record with recurrence
Antineoplastic agents prescribed before n=184
the date of the first diagnosis
Cancer diagnosis other than that described in the inclusion n=44
criteria between the date of the first diagnosis to date of
end of treatment for first relapse

Patients receiving first-line treatment for ovarian, fallopian tube, or peritoneal cancer n=7,839

NAC group (NAC-IDS + chemotherapy only) n=4,182

Excluded
First-line treatment initiation not falling between n=1,318
November 22, 2013, and June 30, 2019

NAC group (all treatment regimens) Analysis of treatment patterns n=2,864

NAC group (TC or TC + Bev as first-line treatment) Analysis of the incidence of adverse events N=1,397 (TC: n=1,131, TC + Bev: n=266)

PDS group n=3,657

Excluded
First-line treatment initiation not falling between n=897
November 22, 2013, and June 30, 2019

PDS group (all treatment regimens) Analysis of treatment patterns n=2,760

PDS group (TC or TC + Bev as first-line treatment) Analysis of the incidence of adverse events N=1,964 (TC: n=1,645, TC + Bev: n=319)

Fig. 1. Flow diagram of patient selection process.
Bev, bevacizumab; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; PDS, primary debulking surgery; TC, paclitaxel + carboplatin.
*Excluded from the analysis if the patient was prescribed only Bev or olaparib as an antineoplastic agent.

group, 140/1,131 (12.4%), 38/347 (11.0%), and 0/530 (0.0%) patients repeated the first-line TC, TC + bevacizumab, and ddTC treatment, respectively, as second-line treatment, and 478/1,203 (39.7%) patients received single-agent chemotherapy, with paclitaxel being the most common drug. The median (95% CI) TFST in the NAC group was 19.2 (15.8–22.6) months in patients receiving bevacizumab and 19.6 (16.7–22.9) months in those not receiving bevacizumab (hazard ratio=1.02; 95% CI=0.85 to 1.22). The annual trend in first-line regimens in the NAC and PDS groups (2013–2019) is summarized in Table S6. TC was the most commonly prescribed first-line treatment in both groups throughout the analyzed years. The proportion of patients receiving TC + bevacizumab as first-line treatment tended to increase in both the NAC (3.3% in 2013; 15.4% in 2019) and PDS (0.0% in 2013; 15.4% in 2019) groups (Table S6).

3. Patient characteristics
The proportion of elderly patients (aged ≥75 years; 7.5% vs. 15.0%) and patients with intestinal obstruction (4.9% vs. 9.2%), intra-abdominal abscess (0.4% vs. 2.3%), and
Bevacizumab for advanced ovarian cancer in Japan

Fig. 2. (A) Details of first-line treatment in the NAC and PDS groups, (B) Sankey diagram for the NAC group (all treatment regimens), and (C) Sankey diagram for the PDS group (all treatment regimens).

Bev, bevacizumab; DC, docetaxel + carboplatin; ddTC, dose-dense paclitaxel + carboplatin; NAC, neoadjuvant chemotherapy; PDS, primary debulking surgery; TC, paclitaxel + carboplatin.

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Bevacizumab for advanced ovarian cancer in Japan

expansory laparotomy (18.0% vs. 25.9%) as medical history or comorbidities was numerically lower in the NAC TC + Bev group (266 patients) versus the NAC TC group (1,131 patients). None of the patients in the NAC TC + Bev group had inflammatory bowel disease (IBD), fistula, or GI perforation. There was no notable difference in the activities of daily living between the NAC TC + Bev and NAC + TC groups (Barthel Index score of 85–100; 81.2% vs. 82.4% [Table 1]).

The proportion of elderly patients (aged ≥75 years; 7.5% vs. 3.4%) and patients with hypertension (23.7% vs. 13.8%) was higher in the NAC TC + Bev group (266 patients) versus the PDS TC + Bev group (319 patients). The proportion of patients with deep vein thrombosis (40.2% vs. 50.2%) and prescriptions of nonsteroidal anti-inflammatory drugs (55.6% vs. 83.7%) was lower in the NAC TC + Bev group versus the PDS TC + Bev group (Table 1).

4. Incidence rates of GI perforation
Five patients (NAC TC + Bev group, 1; NAC TC group, 2; and PDS group receiving TC [hereafter, PDS TC group], 2) met the definition of GI perforation during the first-line treatment period, in whom the occurrence of GI perforation was confirmed by medical expert review (Table S7).

The incidence rate of GI perforation did not show a notable difference between the NAC TC + Bev (0.38% [1/266 patients]) and NAC TC (0.18% [2/1,131 patients]) groups (risk ratio by unadjusted analysis [95% CI], 2.13 [0.19-23.36]; risk difference [95% CI], 0.20 [-0.58 to 0.97]). Consistent results were obtained from the sensitivity analysis using the AIPW

### Table 1. Patient characteristics (data extraction period, April 1, 2008, to January 29, 2020)

| Item                        | NAC (n=1,397) | PDS (n=1,964) | p-value<sup>1</sup> |
|-----------------------------|--------------|---------------|---------------------|
| Age (yr)                    |              |               |                     |
| <65                         | 165 (62.0)   | 669 (59.2)    | 0.003               |
| ≥65 to <75                  | 81 (30.5)    | 292 (25.8)    |                     |
| ≥75                         | 20 (7.5)     | 170 (15.0)    |                     |
| Barthel index score         |              |               | 0.602 <sup>x0.001</sup> |
| 85–100                      | 216 (81.2)   | 932 (82.4)    |                     |
| 60–84                       | 3 (1.1)      | 19 (1.7)      |                     |
| 40–59                       | 1 (0.4)      | 6 (0.5)       |                     |
| 0–39                        | 1 (0.4)      | 14 (1.2)      |                     |
| Missing                     | 45 (16.9)    | 160 (14.1)    |                     |
| Hypertensive disorders      |              |               | 0.087 <sup>x0.003</sup> |
| Intestinal obstruction      | 13 (4.9)     | 104 (9.2)     |                     |
| IBD                         | 0 (0.0)      | 1 (0.1)       |                     |
| Fistula                     | 0 (0.0)      | 2 (0.2)       |                     |
| GI perforation              | 0 (0.0)      | 13 (1.2)      |                     |
| Esophageal, gastric, or duodenal ulcer | 49 (18.4) | 214 (18.9) | 0.931 <sup>x0.512</sup> |
| Diverticulitis              | 2 (0.8)      | 2 (0.2)       |                     |
| Intra-abdominal abscess     | 17 (6.4)     | 71 (6.3)      |                     |
| Deep vein thrombosis        | 107 (40.2)   | 452 (40.0)    |                     |
| Pleural effusion            | 17 (6.4)     | 71 (6.3)      |                     |
| Ascites                     | 53 (19.9)    | 193 (17.1)    |                     |
| NSAID prescriptions         | 148 (55.6)   | 675 (59.7)    |                     |
| Exploratory laparotomy      | 48 (18.0)    | 293 (25.9)    |                     |

Data are presented as number (%). GI, gastrointestinal; IBD, inflammatory bowel disease; NA, not available; NAC, neoadjuvant chemotherapy; NSAID, nonsteroidal anti-inflammatory drug; PDS, primary debulking surgery; TC, paclitaxel + carboplatin; TC + Bev, paclitaxel + carboplatin + bevacizumab.

* NAC group receiving TC + bevacizumab. † NAC group receiving TC (without bevacizumab). ‡ PDS group receiving TC + bevacizumab. § PDS group receiving TC (without bevacizumab). ‖ Fisher’s exact test.
Table 2. Risk difference and risk ratio for the incidence of GI perforation during the first-line treatment period (NAC TC + Bev group vs. NAC TC group)

| Group          | Incidence of GI perforation, % (number/total number) | Unadjusted analysis | Sensitivity analysis (AIPW) |
|----------------|------------------------------------------------------|---------------------|-----------------------------|
|                |                                                     | Risk difference (95% CI) | Risk ratio (95% CI)         |
| NAC TC         | 0.18% (2/1,131)                                     | 0.02 (-0.58 to 0.97)   | 2.13 (0.19 to 23.36)        |
| NAC TC + Bev   | 0.38% (1/266)                                       | 0.17 (-0.32 to 0.95)   | 2.04 (-1.36×10^8 to 9.27)   |

AIPW, augmented inverse propensity weighted; CI, confidence interval; GI, gastrointestinal; NAC, neoadjuvant chemotherapy TC, paclitaxel + carboplatin; TC + Bev, paclitaxel + carboplatin + bevacizumab.

Table 3. Risk difference and risk ratio for the incidence of GI perforation during the first-line treatment period (NAC TC + Bev group vs. PDS TC + Bev group)

| Group          | Incidence of GI perforation, % (number/total number) | Unadjusted analysis | Sensitivity analysis (AIPW) |
|----------------|------------------------------------------------------|---------------------|-----------------------------|
|                |                                                     | Risk difference (95% CI) | Risk ratio (95% CI)         |
| PDS TC + Bev   | 0.00% (0/119)                                       | 0.38 (-0.36 to 1.11)   | NE (NE to NE)               |
| NAC TC + Bev   | 0.38% (1/266)                                       | 0.31 (0.00 to 1.02)    | NE (NE to NE)               |

AIPW, augmented inverse propensity weighted; CI, confidence interval; GI, gastrointestinal; NAC, neoadjuvant chemotherapy; NE, not estimated; PDS, primary debulking surgery; TC, paclitaxel + carboplatin; TC + Bev, paclitaxel + carboplatin + bevacizumab.

5. Incidence rates of AEs other than GI perforation

The incidence rate of esophageal, gastric, or duodenal ulcer was the highest in both the NAC TC + Bev (9.40%, 25/266 patients) and NAC TC (6.01%, 68/1,131 patients) groups, followed by that of venous thrombosis (4.51% [12/266 patients] in the NAC TC + Bev group and 4.69% [53/1,131 patients] in the NAC TC group). The incidence rates were largely similar but were numerically higher in the NAC TC + Bev group versus the NAC + TC group for esophageal, gastric, or duodenal ulcer (9.40% vs. 6.01%) and upper GI bleeding (other than ulcer; 3.01% vs. 0.53%). There was no notable difference in the incidence rates of AEs other than GI perforation between the NAC TC + Bev and PDS TC + Bev groups (Table 4).

6. Post hoc sensitivity analysis of the incidence of GI perforation

By applying the expanded definition and medical expert review, 11 cases of GI perforation (NAC TC + Bev, 1; NAC TC, 5; PDS TC + Bev, 1; and PDS TC, 4) were identified (Table S8). The incidence rate of GI perforation (0.38% [1/266 patients] in the NAC TC + Bev group and 0.44% [5/1,131 patients] in the NAC TC group) did not show a notable difference (risk ratio=0.85; 95% CI=0.10 to 7.25; risk difference=-0.07; 95% CI=-0.90 to 0.76) (Table S9). These findings suggest the appropriateness of the original definition of GI perforation and the robustness of the data derived from it. Similar results were obtained from the comparison between the NAC TC + Bev and PDS TC + Bev groups (Table S10).

**DISCUSSION**

We retrospectively assessed the incidence rate of bevacizumab-associated GI perforation in ovarian cancer using the largest healthcare claims database in Japan. This study is the first to...
assess the incidence of GI perforation associated with NAC containing bevacizumab using healthcare claims data.

The current study revealed that TC and TC + bevacizumab were most commonly used as first-line treatment of ovarian cancer, which is consistent with the recommendations in the 2020 Japan Society of Gynecologic Oncology guidelines [5]. In addition, our results indicate an increasing trend in the use of TC + bevacizumab as first-line treatment for both patients receiving NAC and those receiving PDS for ovarian cancer.

The current findings suggest that bevacizumab is prescribed carefully in Japanese real-world clinical practice to minimize the risk of GI perforation in ovarian cancer, which resulted in a lower incidence of GI perforation than anticipated per previous clinical trial findings. Indeed, the incidence rate of GI perforation requiring surgical intervention (corresponding to grade ≥3 events) observed in the current study (0.38%) is similar to that of grade ≥3 GI perforation reported in JGOG 3022 (0.3%), a prospective, observational study involving 293 Japanese patients with newly diagnosed stage III/IV ovarian cancer [16], but lower than that reported in the GOG 0218 trial (1.6%, 10/608 patients) [17] and the ICON7 trial (1.3%, 10/745 patients) [18]. Moreover, our interrupted time series analysis did not indicate an increase in the incidence rate of GI perforation after the approval of bevacizumab for ovarian cancer in Japan.

Several risk factors for GI perforation associated with bevacizumab use have been identified in previous phase 2 and 3 trials for ovarian cancer, such as a history of 3 prior regimens, bowel wall thickening, intestinal obstruction, IBD treatment, and bowel resection at primary surgery [19,20]. In the current study, the proportion of patients with a history of intestinal obstruction and intra-abdominal abscess was lower in the NAC TC + Bev group versus the

| Table 4. Incidence of adverse events other than GI perforation during the first-line treatment period |
| --- |
| **Adverse event** | **Patients with adverse events, n (%)** | **NAC TC + Bev** | **PDS TC + Bev** | **NAC TC + Bev vs NAC TC** | **Risk difference (95% CI)** | **Risk ratio (95% CI)** | **NAC TC + Bev vs PDS TC + Bev** |
| Fistula | 1 (0.38) | 0 (0.0) | 0 (0.0) | 0.4 (−0.36 to 1.11) | NE (NE to NE) | 0.38 (−0.36 to 1.11) | NE (NE to NE) |
| Cerebral infarction and thromboembolism of cerebrovascular vessels | 2 (0.75) | 3 (0.27) | 1 (0.31) | 0.5 (−0.59 to 1.57) | 2.83 (0.48 to 16.88) | 0.44 (−0.77 to 1.64) | 2.40 (0.22 to 26.31) |
| Angina pectoris | 0 (0.0) | 1 (0.09) | 0 (0.0) | −0.1 (−0.26 to 0.08) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |
| Myocardial infarction | 0 (0.0) | 1 (0.0) | 0 (0.0) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |
| Other acute ischemic heart disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |
| Arterial thrombosis | 0 (0.0) | 3 (0.27) | 0 (0.0) | −0.3 (−0.57 to 0.03) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |
| Venous thrombosis | 12 (4.51) | 53 (4.69) | 6 (1.88) | −0.2 (−0.26 to 0.17) | 0.96 (0.52 to 1.78) | 0.44 (0.22 to 0.91) | 0.89 (0.40 to 2.01) |
| Pulmonary embolism | 3 (1.13) | 20 (1.77) | 1 (0.94) | −0.6 (−0.12 to 0.88) | 0.64 (0.19 to 2.13) | 1.20 (0.24 to 5.89) | 1.20 (0.24 to 5.89) |
| Intracranial hemorrhage | 1 (0.38) | 2 (0.18) | 0 (0.0) | 0.2 (−0.58 to 0.97) | 2.13 (0.19 to 21.36) | 0.38 (−0.36 to 1.11) | NE (NE to NE) |
| Esophageal, gastric, or duodenal ulcer | 25 (9.40) | 68 (6.01) | 21 (6.58) | 3.4 (−0.38 to 7.16) | 1.56 (1.01 to 2.42) | 2.82 (−0.62 to 7.25) | 1.43 (0.82 to 2.49) |
| Upper GI bleeding (other than ulcer) | 8 (3.01) | 6 (0.53) | 3 (0.94) | 2.5 (0.38 to 4.57) | 5.67 (1.98 to 16.20) | 2.07 (−0.24 to 4.38) | 3.20 (0.86 to 11.93) |
| Lower GI bleeding (including ulcer) | 0 (0.0) | 2 (0.18) | 0 (0.0) | −0.2 (−0.42 to 0.07) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |
| Other GI bleeding (no distinction between upper/lower GI bleeding) | 0 (0.0) | 2 (0.18) | 0 (0.0) | −0.2 (−0.42 to 0.07) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |
| Intestinal pneumonia | 0 (0.0) | 2 (0.18) | 0 (0.0) | −0.2 (−0.42 to 0.07) | NE (NE to NE) | NE (NE to NE) | NE (NE to NE) |

Values are presented as number (%) not otherwise specified.
CI, confidence interval; GI, gastrointestinal; NAC, neoadjuvant chemotherapy; NE, not estimated; PDS, primary debulking surgery; TC, paclitaxel + carboplatin; TC + Bev, paclitaxel + carboplatin + bevacizumab.

*NAC group receiving TC + bevacizumab. †NAC group receiving TC (without bevacizumab). ‡PDS group receiving TC + bevacizumab.
NAC TC group, and none of the patients in the NAC TC + Bev group had a history of IBD, fistula, or GI perforation. These findings indicate that in Japan, bevacizumab use is avoided in patients with risk factors for GI perforation. Nevertheless, GI perforation still warrants special attention because 1 death due to this event (a patient with diffuse involvement of both the large and small bowels) was reported among 25 patients with unresectable advanced ovarian cancer receiving NAC with bevacizumab [21].

By using a healthcare claims database, this study was able to assess the treatment pattern and bevacizumab-associated AE profile in Japanese patients with ovarian cancer in real-world clinical practice, which can be extrapolated to patients in the Asia-Pacific region. The strength of this study is that it included the largest number of patients with ovarian cancer to date by using a healthcare claims database. Additionally, data review by medical experts contributed to the enhanced accuracy of GI perforation cases identified by prespecified definitions. However, this study has some limitations. We focused on GI perforation requiring surgical intervention but did not capture grade 1 or 2 events or patients without medical practice records for GI perforation treatment. Notably, medical expert review of patients with ICD-10 codes pertaining to GI perforation without medical practice performed (i.e., grade 1 or 2 events) did not identify patients with GI perforation. Moreover, the differences and similarities in patient characteristics between the groups compared may have not been completely evaluated because several key patient characteristics were not captured in the current study. Thus, the patient characteristics were not completely matched between the NAC and PDS groups, making the data interpretation difficult.

In conclusion, we observed no notable association between bevacizumab use and the incidence rates of GI perforation in patients with ovarian, fallopian tube, or peritoneal cancer receiving NAC. Our results suggest that in routine clinical practice in Japan, bevacizumab is prescribed with sufficient care to avoid GI perforation.

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SUPPLEMENTARY MATERIALS

Table S1
ICD-10 codes used for patient record extraction

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**Table S2**  
Medical practice categories used for the definition of GI perforation  
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**Table S3**  
List of AEs other than GI perforation  
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**Table S4**  
List of basic regimens  
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**Table S5**  
List of medical practice categories used for the expanded definition of GI perforation  
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**Table S6**  
Annual trend in the prescription of first-line treatment for ovarian cancer  
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**Table S7**  
Incidence of GI perforation during the first-line treatment period  
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**Table S8**  
Incidence of GI perforation during the first-line treatment period using the expanded definition  
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**Table S9**  
Risk difference and risk ratio for the incidence of GI perforation during the first-line treatment period using the expanded definition (NAC TC + Bev group vs. NAC TC group)  
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**Table S10**  
Risk difference and risk ratio for the incidence of GI perforation during the first-line treatment period using the expanded definition (NAC TC + Bev group vs. PDS TC + Bev group)  
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Fig. S1
Interrupted time series analysis for the incidence of GI perforation before and after the approval of bevacizumab for ovarian cancer in Japan.

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REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941-53.
2. National Cancer Center Japan; Center for Cancer Control and Information Services. Projected cancer statistics [Internet]. Tokyo: National Cancer Center Japan; 2022 [cited 2022 Apr 21]. Available from: https://ganjoho.jp/reg_stat/statistics/stat/short_pred_en.html.
3. Japan Society of Obstetrics and Gynecology. Patient annual report and treatment annual report [in Japanese]. Treatment Annual Report for 2013 [Internet]. Tokyo: Japan Society of Obstetrics and Gynecology; 2022 [cited 2022 Apr 21]. Available from: https://www.jsog.or.jp/modules/committee/index.php?content_id=7#databook.
4. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakhht K, Berchuck A, et al. Ovarian cancer, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021;19:191-226.
5. Tokunaga H, Mikami M, Nagase S, Kobayashi Y, Tabata T, Kaneuchi M, et al. The 2020 Japan Society of Gynecologic Oncology guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer. J Gynecol Oncol 2021;32:e49.
6. Rouzier R, Gouy S, Selle F, Lambaudie E, Floquet A, Fourchotte V, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: results from the ANTHALYA trial. Eur J Cancer 2017;70:133-42.
7. Garcia Garcia Y, de Juan Ferré A, Mendiola C, Barretina-Ginesta MP, Gaba Garcia L, Santaballa Bertrán A, et al. Efficacy and safety results from GEICO 1205, a randomized phase II trial of neoadjuvant chemotherapy with or without bevacizumab for advanced epithelial ovarian cancer. Int J Gynecol Cancer 2019;29:1050-6.
8. Daniele G, Lorusso D, Scambia G, Cecere SC, Nicoletto MO, Breda E, et al. Feasibility and outcome of interval debulking surgery (IDS) after carboplatin-paclitaxel-bevacizumab (CPB): a subgroup analysis of the MITO-16A-MaNGO OV2A phase 4 trial. Gynecol Oncol 2017;144:256-9.
9. Komiyama S, Kugimiya T, Kubushiro K. Safety and efficacy of neoadjuvant chemotherapy containing bevacizumab and interval debulking surgery for advanced epithelial ovarian cancer: a feasibility study. J Surg Oncol 2018;118:687-93.
10. Kusunoki S, Terao Y, Hirayama T, Fujino K, Ujihira T, Ota T, et al. Safety and efficacy of neoadjuvant chemotherapy with bevacizumab in advanced-stage peritoneal/ovarian cancer patients. Taiwan J Obstet Gynecol 2018;57:650-3.
11. Majid N, Ghissassi I, Mrabti H, Errihani H. Bevacizumab in clinical practice. Gulf J Oncolog 2015;1:33-7.
12. Sato S, Itamochi H. Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy. Ther Adv Med Oncol 2014;6:293-304.
13. Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? Gynecol Oncol 2007;105:3-6.
14. Choi YI, Lee SH, Ahn BK, Baek SU, Park SJ, Kim YS, et al. Intestinal perforation in colorectal cancers treated with bevacizumab (Avastin). Cancer Res Treat 2008;40:33-5.
15. Medical Data Vision Co. Ltd. About MDV database [Internet]. Tokyo: Medical Data Vision Co. Ltd.; 2022 [cited 2022 Apr 21]. Available from: https://en.mdv.co.jp/about-mdv-database/.

16. Komiyama S, Kato K, Inokuchi Y, Takano H, Matsumoto T, Hongo A, et al. Bevacizumab combined with platinum-taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients (JGOG3022 trial). Int J Clin Oncol 2019;24:103-14.

17. National Institute for Health and Clinical Excellence. Single technology appraisal (STA): bevacizumab in combination with carboplatin and paclitaxel for the treatment of advanced ovarian cancer, August 2012 [Internet]. London: National Institute for Health and Clinical Excellence; 2022 [cited 2022 Apr 21]. Available from: https://www.nice.org.uk/guidance/ta284/documents/ovarian-cancer-metastatic-bevacizumab-with-paclitaxel-and-carboplatin-manufacturer-submission-roche2.

18. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.

19. Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180-6.

20. Burger RA, Brady MF, Bookman MA, Monk BJ, Walker JL, Homesley HD, et al. Risk factors for GI adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2014;32:1210-7.

21. Petrillo M, Paris I, Vizzielli G, Amadio G, Cosentino F, Salutari V, et al. Neoadjuvant chemotherapy followed by maintenance therapy with or without bevacizumab in unresectable high-grade serous ovarian cancer: a case-control study. Ann Surg Oncol 2015;22 Suppl 3:S952-8.