The efficacy and safety profile of 2-weekly dosing of bevacizumab-containing chemotherapy for platinum-resistant recurrent ovarian cancer

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Abstract
Background  Despite being widely used, to date (June 2021), the regimen of bevacizumab 10 mg/kg every 2 weeks (Q2W) combined with chemotherapy is not approved in Japan for patients with platinum-resistant recurrent ovarian cancer. In this retrospective analysis, we evaluated the usage patterns of bevacizumab administered for platinum-resistant recurrent ovarian cancer.

Methods  We obtained clinical data from 155 Japanese medical facilities between November 2013 and December 2018 via a survey. Items included the number of cases of platinum-resistant recurrent ovarian cancer treated with bevacizumab according to dosage. For regimens including bevacizumab 10 mg/kg Q2W, additional information was requested relating to concomitantly administered agents, and the efficacy and safety of the regimen.

Results  Of 1739 bevacizumab-containing regimens reported in 1633 patients with recurrent ovarian cancer, 264 used 10 mg/kg Q2W. The overall response rate (ORR) with this regimen was 26.1%. Response rates varied according to regimen and were particularly favorable when bevacizumab 10 mg/kg Q2W was administered with paclitaxel (ORR, 53.0%) versus liposomal doxorubicin (15.0%; P < 0.0001) and irinotecan (7.7%; P < 0.028). The most frequent Grade ≥ 3 adverse events associated with bevacizumab 10 mg/kg Q2W were neutropenia (11.7%) and hypertension (11.7%). The most frequent bevacizumab-associated Grade ≥ 3 adverse events with bevacizumab plus paclitaxel versus bevacizumab plus liposomal doxorubicin were hypertension (9.0% versus 13.9%) and proteinuria (3.0% versus 8.4%).

Conclusions  Bevacizumab 10 mg/kg Q2W appears efficacious for patients with recurrent ovarian cancer, with a manageable toxicity profile. Approval of this regimen is clinically desirable for Japanese patients with ovarian cancer.

Keywords  Bevacizumab · Drug-related side effects and adverse reactions · Drug therapy · Ovarian neoplasms

Introduction

According to the World Health Organization, in 2020 there were 10,964 new cases of ovarian cancer diagnosed in Japan and 5302 deaths from the disease [1]. The incidence of ovarian cancer is increasing [2, 3], and its mortality exceeds that of any other type of gynecologic cancer [1, 2]. Ovarian cancer is usually treated with surgery combined with chemotherapy [2], but many patients develop recurrence due to residual micrometastases even after macroscopic complete remission is achieved [4, 5]. Recurrence occurs in 55% of
patients with late-stage ovarian cancer (stage III and stage IV) within 2 years and in 70% within 5 years [6].

For patients who develop recurrence within 6 months of their final treatment, platinum-based chemotherapy is not recommended [7]. For patients with platinum-resistant disease, bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has demonstrated antitumor activity [7, 8]. Bevacizumab has been approved in several countries to be used in combination with chemotherapy, followed by maintenance monotherapy [9–11].

The efficacy and safety of bevacizumab (at doses of 15 mg/kg every 3 weeks [Q3W] or 10 mg/kg every 2 weeks [Q2W]) combined with chemotherapy were demonstrated in patients with platinum-resistant recurrent ovarian cancer in the phase III AURELIA trial conducted in Europe [12]. Although both of these dosing regimens have been approved in Europe and North America [9, 10], only the 15 mg/kg dose Q3W or longer has been approved in Japan [11]. Nonetheless, despite the lack of official approval, bevacizumab 10 mg/kg Q2W is used in actual clinical practice in Japan, because the chemotherapy regimen for platinum-resistant recurrent ovarian cancer is typically every 2 or 4 weeks; thus, the Q2W administration of bevacizumab is easy to implement for oncologists and their patients. Moreover, bevacizumab 10 mg/kg Q2W in combination with carboplatin and pegylated liposomal doxorubicin was shown to be efficacious in a group of patients with platinum-sensitive recurrent ovarian cancer in the recently published AGO-OVAR 2.21 trial [13]. As a result, the Q2W regimen is widely cited in textbooks [14, 15] and guidelines [7, 16, 17] both in Japan and overseas.

We conducted a real-world analysis of Japanese clinical practice to reveal the usage patterns of bevacizumab for platinum-resistant recurrent ovarian cancer, and to examine the efficacy and safety of bevacizumab 10 mg/kg Q2W.

Materials and methods

Study design

This was a retrospective analysis of clinical practices within Japan; no patient identifying data were collected, and no interventions or procedures were mandated. This study was approved by the Ethics Committee of the primary study facility (Niigata University, Niigata, Japan) and the Ethics Committees of all other participating facilities.

A questionnaire was sent by postal mail to 388 medical facilities across Japan between October 2018 and December 2018. Information was requested on the usage patterns of bevacizumab administered for platinum-resistant recurrent ovarian cancer between November 2013 and December 2018. The selection of facilities to which questionnaires were sent was based on their identification as a workplace for specialists certified by the Japan Society of Gynecologic Oncology, and where bevacizumab was likely to be offered as a treatment for patients with ovarian cancer.

Survey items

The items in the questionnaire included the total number of cases of platinum-resistant recurrent ovarian cancer treated with bevacizumab and the number of cases according to bevacizumab dosage. For regimens including bevacizumab 10 mg/kg Q2W, additional information was requested on the types and dosages of concomitantly administered anti-cancer agents, the efficacy of the treatment regimen (based on the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), and the safety of the regimen (based on adverse events [AEs]).

Data analysis

As this analysis was not designed to statistically test a hypothesis, no power calculations were performed. All data collected were summarized descriptively. We used R version 3.4.1 (Vienna, Austria) to calculate Fisher’s exact test, and a two-sided P value of <0.05 was considered to indicate statistical significance.

Results

Bevacizumab regimens used in real-world clinical practice

Of the 388 facilities who were sent the questionnaire, 155 provided a response (39.9% response rate). Treatment details were received for 1633 patients with recurrent ovarian cancer; the total number of bevacizumab regimens administered was 1739 (Table 1). The most common regimen was 15 mg/kg Q3W (997 regimens), followed by 15 mg/kg every 4 weeks (476 regimens). Of the 155 facilities which responded, 41 (26.5%) were using the dosage of interest (10 mg/kg Q2W); overall, this dosage was used in 264 regimens in 264 patients.

As shown in Table 1, the agents most commonly administered alongside bevacizumab (any regimen) were paclitaxel (613 regimens) and liposomal doxorubicin (602 regimens). Bevacizumab 10 mg/kg Q2W was administered most frequently with liposomal doxorubicin (176 regimens), paclitaxel (73 regimens), irinotecan (16 regimens), or gemcitabine (7 regimens). The most common regimens for each concomitant agent were as follows: liposomal doxorubicin 40 mg/m², administered on day 1 of a 4-week cycle (n/N = 166/176); paclitaxel 80 mg/m², administered on
day 1 of a 1-week cycle \((n/N = 68/73)\); irinotecan 70 mg/m\(^2\), administered on days 1, 8, and 15 of a 4-week cycle \((n/N = 7/16)\); and gemcitabine 1000 mg/m\(^2\), administered on days 1 of a 2-week cycle \((n/N = 5/7)\).

### Response rates with bevacizumab 10 mg/kg Q2W

Table 2 shows the best overall response achieved with bevacizumab 10 mg/kg Q2W for platinum-resistant recurrent ovarian cancer, based on RECIST v1.1 criteria; the overall response rate (ORR) with this regimen was 26.1%. Rates varied according to the combination regimen used and were particularly favorable when bevacizumab 10 mg/kg Q2W was combined with paclitaxel (ORR, 53.0%) versus liposomal doxorubicin (15.0%; \(P < 0.0001\)) and irinotecan (7.7%; \(P < 0.028\)).

Overall, there were 4 complete responses (bevacizumab plus liposomal doxorubicin, \(n = 3\); bevacizumab plus paclitaxel, \(n = 1\)) and 65 partial responses (including 22 with bevacizumab plus liposomal doxorubicin and 34 with bevacizumab plus paclitaxel). The disease control rate (complete response + partial response + stable disease) was 52.3% with bevacizumab 10 mg/kg Q2W; this varied from 75.8% when bevacizumab was combined with paclitaxel to 15.4% when combined with irinotecan.

### Safety profile of bevacizumab 10 mg/kg Q2W

AEs of Grade \(\geq 3\) occurring in \(\geq 1\%\) of patients receiving bevacizumab 10 mg/kg Q2W are shown in Table 3. Overall, 154 AEs of Grade \(\geq 3\) were reported with bevacizumab 10 mg/kg Q2W. The most frequent were neutropenia \((n = 31 [11.7\%])\), hypertension \((n = 31 [11.7\%])\), proteinuria \((n = 16 [6.1\%])\), and anemia \((n = 14 [5.3\%])\). Most \((n = 134)\) were Grade 3; only a single Grade 5 event was reported, which was acute respiratory distress syndrome.

The safety profile (Grade \(\geq 3\) AEs) with bevacizumab 10 mg/kg Q2W according to combination regimen (bevacizumab plus liposomal doxorubicin versus bevacizumab plus paclitaxel) is shown in Table 4. For bevacizumab plus liposomal doxorubicin versus bevacizumab plus paclitaxel, 118 versus 29 AEs of Grade \(\geq 3\) were reported, and the

### Table 1

Regimens of bevacizumab used in real-world clinical practice to treat platinum-resistant recurrent ovarian cancer

| Regimen, \(n\) | Agents combined with bevacizumab | Overall number of regimens\(^b\) |
|---------------|---------------------------------|-------------------------------|
|               | Liposomal doxorubicin | Paclitaxel | Gemcitabine | Topotecan | Other\(^a\) |  |
| Total         | 602                      | 613        | 284         | 182       | 214       | 1739   |
| 15 mg/kg every 3 weeks | 209                     | 429        | 233         | 130       | 127       | 997    |
| 15 mg/kg every 4 weeks | 217                     | 111        | 44          | 52        | 61        | 476    |
| 10 mg/kg every 2 weeks | 176                     | 73         | 7           | 0         | 24\(^c\)   | 264    |
| Other\(^d\)   | 0                        | 0          | 0           | 0         | 2         | 2      |

\(^a\)Including bevacizumab monotherapy

\(^b\)When several regimens were used for a single patient, those regimens were counted individually

\(^c\)Irinotecan \((n = 16)\), cisplatin \((n = 7)\), and carboplatin \((n = 1)\)

\(^d\)15 mg/kg administered on a flexible schedule every 3 or 4 weeks according to the condition of the patient

### Table 2

Efficacy of bevacizumab 10 mg/kg every 2 weeks for platinum-resistant recurrent ovarian cancer (based on the Response Evaluation Criteria in Solid Tumors version 1.1)

| Best overall response, \(n (\%)\) | Agents combined with bevacizumab\(^b\) | All bevacizumab 10 mg/kg \((n = 264)\) |
|-------------------------------|---------------------------------|---------------------------------|
|                               | Liposomal doxorubicin \((n = 167)\) | Paclitaxel \((n = 66)\) | Irinotecan \((n = 13)\) |
| Complete response             | 3 (1.8)                          | 1 (1.5)                        | 0                  | 4 (1.5) |
| Partial response              | 22 (13.2)                        | 34 (51.5)                      | 1 (7.7)            | 65 (24.6) |
| Overall response rate\(^b\)  | 25 (15.0)                        | 35 (53.0)                      | 1 (7.7)            | 69 (26.1) |
| Stable disease                | 49 (29.3)                        | 15 (22.7)                      | 1 (7.7)            | 69 (26.1) |
| Disease control rate\(^c\)   | 74 (44.3)                        | 50 (75.8)                      | 2 (15.4)           | 138 (52.3) |
| Progressive disease           | 74 (44.3)                        | 13 (19.7)                      | 7 (53.8)           | 99 (37.5) |
| Not assessed/unknown          | 19 (11.4)                        | 3 (4.5)                        | 4 (30.8)           | 27 (10.2) |

\(^a\)Data for the best overall response achieved without switching agents is presented

\(^b\)Complete response + partial response

\(^c\)Complete response + partial response + stable disease
### Discussion

Although the regimen of bevacizumab 10 mg/kg Q2W is not yet (as of June 2021) approved for treatment of platinum-resistant ovarian cancer in Japan, our data indicate that such a regimen is used in around 15% (264/1739) of bevacizumab treatment regimens in this patient population. The chemotherapeutic agents most frequently combined with bevacizumab 10 mg/kg Q2W were liposomal doxorubicin and paclitaxel; this is consistent with the agents used in the phase III AURELIA trial [12]. However, unlike the AURELIA trial, no patients in our analysis were found to have received bevacizumab 10 mg/kg Q2W plus topotecan. This is likely because topotecan has dose-limiting myelosuppressive effects [18], and Japanese clinicians prefer to use an alternative topoisomerase I inhibitor, irinotecan.

Our investigation of the efficacy of bevacizumab 10 mg/kg Q2W in ovarian cancer found that the ORR for this regimen was 26.1%. This was in line with the data reported from the AURELIA trial, where the ORR with bevacizumab 10 mg/kg Q2W plus chemotherapy was 27.3% [12], and with the data from a phase II study of bevacizumab 10 mg/kg Q2W plus topotecan, where the ORR was 25.0% [19]. The present study also indicated wide differences in the ORR depending on the combination chemotherapy agent used (53.0% with paclitaxel, 15.0% with liposomal doxorubicin, 7.7% with irinotecan) with a significantly higher response rate for the paclitaxel combination compared with liposomal doxorubicin ($P < 0.0001$) and irinotecan ($P < 0.028$). Similar differences in efficacy according to the chemotherapeutic agent administered alongside bevacizumab 10 mg/kg Q2W were reported in a recent study in Korea [20], indicating that the choice of combination chemotherapy must be a key consideration in clinical practice. In the AURELIA trial, of the chemotherapeutic agents used in combination with bevacizumab 10 mg/kg Q2W, only liposomal doxorubicin was used at the dosage approved in Japan [12]; thus, further investigation of the optimal combination regimen in Japanese patients is warranted.

The occurrence of Grade ≥ 3 AEs in phase III clinical trials of bevacizumab in advanced ovarian cancer was evaluated in a previously published systematic review [21], with hypertension, thromboembolic events, proteinuria, bleeding and gastrointestinal events found to occur at a higher incidence with bevacizumab than in the control groups. Similar data were reported in Japan for the dosages of 15 mg/kg Q3W (approved for ovarian cancer) and 10 mg/kg Q2W (approved for colorectal cancer, non-small cell lung cancer, breast cancer, malignant glioma, and cervical cancer) [11]. An updated evaluation, including data

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**Table 3** Adverse events of Grade ≥ 3 occurring in ≥ 1% of patients receiving bevacizumab 10 mg/kg every 2 weeks ($n = 264$)

| Adverse event, % | All events of Grade ≥ 3 | Grade 3 | Grade 4 |
|------------------|-------------------------|---------|---------|
| Any adverse event| 154 (58.3)              | 134 (50.8) | 19 (7.2) |
| Hematologic toxicities |                        |         |         |
| Neutropenia      | 31 (11.7)               | 23 (8.7) | 8 (3.0) |
| Anemia           | 14 (5.3)                | 14 (5.3) | 0       |
| Thrombocytopenia | 7 (2.7)                 | 6 (2.3)  | 1 (0.4) |
| Febrile neutropenia | 3 (1.1)             | 3 (1.1)  | 0       |
| Non-hematologic toxicities |                    |         |         |
| Hypertension     | 31 (11.7)               | 31 (11.7) | 0       |
| Proteinuria      | 16 (6.1)                | 16 (6.1) | 0       |
| Hand–foot syndrome | 6 (2.3)              | 6 (2.3)  | 0       |
| Ileus            | 5 (1.9)                 | 4 (1.5)  | 1 (0.4) |
| Gastrointestinal perforation | 4 (1.6)          | 0       | 4 (1.2) |
| Venous thrombosis $^b$ | 4 (1.6)           | 4 (1.6)  | 0       |
| Mucositis        | 3 (1.1)                 | 3 (1.1)  | 0       |

Adverse events were categorized according to the Preferred Terms of the Medical Dictionary for Regulatory Activities version 21.1 and graded according to the Common Terminology Criteria for Adverse Events version 4.0

$^a$Only one Grade 5 event (0.4%) was reported: acute respiratory distress syndrome

$^b$Includes pulmonary embolism

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**Table 4** Adverse events of Grade ≥ 3 occurring with bevacizumab 10 mg/kg every 2 weeks according to combination regimen (bevacizumab plus liposomal doxorubicin versus bevacizumab plus paclitaxel)

| Adverse event, % | Events of Grade ≥ 3 occurring with bevacizumab | With liposomal doxorubicin (n = 167) | With paclitaxel (n = 66) | All (n = 264) |
|------------------|-----------------------------------------------|------------------------------------|--------------------------|--------------|
| Any adverse event| 118 (70.7)                                   | 29 (43.9)                          | 154 (58.3)               |
| Hypertension     | 24 (13.9)                                    | 6 (9.0)                            | 31 (11.7)                |
| Proteinuria      | 14 (8.4)                                     | 2 (3.0)                            | 16 (6.1)                 |
| Gastrointestinal perforation | 2 (1.2)                               | 2 (3.0)                            | 4 (1.6)                  |
| Venous thrombosis $^a$ | 2 (1.2)                                 | 2 (3.0)                            | 4 (1.6)                  |

Adverse events were categorized according to the Preferred Terms of the Medical Dictionary for Regulatory Activities version 21.1 and graded according to the Common Terminology Criteria for Adverse Events version 4.0

$^a$Includes pulmonary embolism

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Most frequent bevacizumab-associated Grade ≥ 3 AEs were hypertension ($n = 24$ [13.9%] versus $n = 6$ [9.0%], respectively) and proteinuria ($n = 14$ [8.4%] versus $n = 2$ [3.0%], respectively).
from the AURELIA [12] and GOG-0218 [22] studies, plus data from the recent JGOG3022 study in Japanese patients [23], is shown in Table 5. Notably, lower rates of hypertension and higher rates of proteinuria were observed in the Japanese patients in the JGOG3022 study compared with the Western patients in the phase III trials; a similar tendency was observed in the current analysis. Overall, however, the safety profile of bevacizumab 10 mg/kg Q2W for ovarian cancer found in the present study was consistent with previous reports, with generally low rates of gastrointestinal perforation, venous thrombosis, fistula, and bleeding, and the majority of the toxicities reported can be adequately managed by gynecologic oncologists [24].

When the rate of bevacizumab-associated AEs was compared between different chemotherapeutic combinations, a slightly higher rate of Grade ≥ 3 hypertension was found to be associated with bevacizumab plus liposomal doxorubicin (13.9%) compared with bevacizumab plus paclitaxel (9.0%); however, incidences of proteinuria, deep vein thrombosis, and gastrointestinal perforation were similar between regimens. Therefore, depending on the concomitant agents administered with bevacizumab, physicians should take appropriate precautions and implement suitable monitoring. For patients who receive a bevacizumab 10 mg/kg Q2W regimen, paclitaxel is most likely to be administered once weekly and AEs can be identified early in the course of treatment; this early identification and amelioration likely contributes to the small numbers of Grade ≥ 3 AEs reported in this analysis. Based on the reported safety profiles for liposomal doxorubicin [25] and paclitaxel [26] in Japanese patients, hypertension (all grades) would be expected to occur in 5.4% and 12.7% of treated patients, respectively, and Grade ≥ 3 hypertension in 0% and 1.1%, respectively. Notably, hypertension occurs more frequently in Japanese patients receiving weekly paclitaxel. There are no clear differences in the frequency of proteinuria expected with liposomal doxorubicin and paclitaxel in Japanese patients, with all grade events observed in 13.5% and 12.7%, respectively, and Grade ≥ 3 proteinuria in 0% and 0.6%, respectively.

Together, the results of our study showed that Japanese oncologists use a variety of chemotherapeutic agents for platinum-resistant ovarian cancer combined with bevacizumab 10 mg/kg Q2W, and the efficacy and safety of each combination vary considerably. Overall, however, the data indicate that bevacizumab 10 mg/kg Q2W can be efficacious for patients with recurrent ovarian cancer and has a well-understood toxicity profile which can be managed by clinicians. The approval of this dosage regimen in Japan is keenly awaited, as it is well suited for clinical practice, and may reduce the treatment burden on patients by streamlining hospital visits. Once approved, bevacizumab 10 mg/kg Q2W will offer patients with platinum-resistant ovarian cancer more treatment choices, and in the future it may be used in new combination therapies with approved or developmental agents in Japan.

The study has some limitations which must be considered. First, this was a questionnaire survey which included selected medical facilities. Although the institutions invited to participate were those expected to have a high volume of bevacizumab-treated patients, we cannot

| Table 5 | Summary of selected adverse events occurring with bevacizumab in the present analysis compared with previously published studies |
|---------|---------------------------------------------------------------------------------------------------------------------------------|
| Bevacizumab dose | Current analysis* | AURELIA [12]a | GOG-0218 [22]b | JGOG3022 [23]a |
| Bevacizumab 10 mg/kg Q2W | 15 mg/kg Q3W | 15 mg/kg Q3W | 15 mg/kg Q3W | 15 mg/kg Q3W |
| Analysis group | All patients (n = 264) | Bevacizumab plus chemotherapyc (n = 179) | Bevacizumab plus paclitaxel and carboplatin (n = 607) | Maintenance bevacizumab (n = 608) | Bevacizumab plus paclitaxel and carboplatin (n = 293) | Maintenance bevacizumab (n = 293) |
| Adverse event, % | | | | | |
| Hypertension | 11.7 | 7.3 | 16.5 | 22.9 | 14.0 | 9.2 |
| Proteinuria | 6.1 | 1.7 | 0.7 | 1.6 | 2.7 | 9.9 |
| GI events | – | – | 2.8 | 2.6 | – | – |
| Perforation | 1.6 | 1.7 | – | – | 0 | 0.3 |
| Fistula | 0 | 1.1 | – | – | 0.3 | 0.3 |
| Venous thrombosis | 1.6 | 2.8 | 5.3 | 6.7 | 0.7 | 0.7 |
| Bleeding | 0 | 1.1 | 1.3 | 2.1 | 0 | 0 |

GI gastrointestinal; Q2W every 2 weeks; Q3W every 3 weeks
*Includes adverse events of Grade ≥ 3 only
bEvents of Grade ≥ 2 were reported for hypertension; events of Grade ≥ 3 for proteinuria and bleeding; and all grade events for other items
cEither pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan
be certain that the data reported are representative of all ovarian cancer treatment across Japan. Second, it is possible that our data are biased in favor of sites who used bevacizumab 10 mg/kg Q2W. The rate of collected questionnaires was not as high as we would have wished (39.9%); however, more than one-quarter of sites which responded were found to have experience of administering bevacizumab 10 mg/kg Q2W. Moreover, to participate in this study, sites were required to obtain ethical approval, and sites which did not use this regimen may have been less likely to apply for ethical approval and respond to the questionnaire. Third, as we asked physicians only about the efficacy and safety of bevacizumab 10 mg/kg administered Q2W, and we did not collect efficacy/safety data relating to the dose of 15 mg/kg administered Q3W, we are unable to make any direct comparisons between these regimens. In addition, we did not request the full clinical details for each patient, so although we were able to assess response rates, we are unable to speculate on survival durations associated with the bevacizumab 10 mg/kg Q2W treatment regimen. Similarly, although a Grade 5 AE was reported and its causal relationship to bevacizumab treatment could not be ruled out, no additional details were available for a fuller evaluation.

In conclusion, this study found that the use of a non-approved dose of bevacizumab (10 mg/kg Q2W) for platinum-resistant recurrent ovarian cancer in real-world clinical practice in Japan provided an antitumor effect and had a safety profile similar to those previously reported for this dose in studies conducted outside Japan. These findings support the use of bevacizumab 10 mg/kg Q2W for the treatment of recurrent ovarian cancer, and we believe that implementing this regimen may have beneficial effects on patients’ lives.

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Declarations

Conflict of interest Masayuki Sekine has received honoraria from AstraZeneca K.K. Takayuki Enomoto has received honoraria from AstraZeneca K.K. and Chugai Pharmaceutical Co., Ltd. Daisuke Aoki has received honoraria from Chugai Pharmaceutical Co., Ltd. Yoh Watanabe, Hidetaka Katauchi, and Nobuo Yaegashi have no conflict of interest. The authors confirm that they have full control of all primary data, and they agree to allow the journal to review their data if requested.

Ethical approval This study was approved by the Ethics Committee of the primary study facility (Niigata University, Niigata, Japan) and the Ethics Committees of all other participating facilities.

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References

1. International Agency for Research on Cancer, World Health Organization (2020) Globocan 2020 Cancer Fact Sheets: Japan. Available at https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf. Accessed Feb 2021
2. Yamagami W, Nagase S, Takahashi F et al (2017) Clinical statistics of gynecologic cancers in Japan. J Gynecol Oncol 28(2):e32
3. Coburn SB, Bray F, Sherman ME et al (2017) International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer 140(11):2451–2460
4. Henmssy BT, Coleman RL, Markman M (2009) Ovarian cancer. Lancet 374(9698):1371–1382
5. Jelovac D, Armstrong DK (2011) Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin 61(3):183–203
6. Heintz AP, Odicino F, Maisonneuve P et al (2006) Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95(Suppl):S161-192
7. National Comprehensive Cancer Network (2020) NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer version 2.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed Feb 2021
8. McClung EC, Wenham RM (2016) Profile of bevacizumab in the treatment of platinum-resistant ovarian cancer: current perspectives. Int J Womens Health 8:59–75
9. Genentech Inc. (2021) AVASTIN (bevacizumab) injection, for intravenous use. Prescribing information. Available at https://www.gene.com/download/pdf/avastin_prescribing.pdf. Accessed Feb 2021
10. Roche Pharma AG (2015) Avastin 25 mg/ml concentrate for solution for infusion. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. Accessed Feb 2021
11. Chugai Pharmaceutical Co. Ltd. (2020) AVASTIN for intravenous infusion. Package insert (in Japanese). Available at https://www.info.pmda.go.jp/go/pack/4291413A1022_1_23/. Accessed Feb 2021
12. Pujade-Lauraine E, Hilpert F, Weber B et al (2014) Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 32(13):1302–1308
13. Pfisterer J, Shannon CM, Baumann K et al (2020) Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, open-label, phase 3 trial. Lancet Oncol 21(5):699–709
14. DeVita VT, Lawrence TS, Rosenberg SA (2014) DeVita, Hellman, and Rosenberg’s Cancer: principles & practice of oncology (cancer principles and practice of oncology), 10th edn. Wolters Kluwer, Philadelphia
15. Japanese Society of Clinical Oncology (2015) New clinical oncology: revised 4th Edition [新臨床腫瘍学改訂第4版] (in Japanese). JCOG, Japan

16. Ledermann JA, Raja FA, Fotopoulou C et al (2013) Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi24-32

17. Komiyama S, Katabuchi H, Mikami M et al (2016) Japan Society of Gynecologic Oncology guidelines 2015 for the treatment of ovarian cancer including primary peritoneal cancer and fallopian tube cancer. Int J Clin Oncol 21(3):435–446

18. Hartmann JT, Lipp HP (2006) Camptothecin and podophyllotoxin derivatives: inhibitors of topoisomerase I and II - mechanisms of action, pharmacokinetics and toxicity profile. Drug Saf 29(3):209–230

19. McGonigle KF, Muntz HG, Vuky J et al (2011) Combined weekly topotecan and biweekly bevacizumab in women with platinum-resistant ovarian, peritoneal, or fallopian tube cancer: results of a phase 2 study. Cancer 117(16):3731–3740

20. Lee JY, Park JY, Park SY et al (2019) Real-world effectiveness of bevacizumab based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA): A Korean Gynecologic Oncology Group study (KGOG 3041). Gynecol Oncol 152(1):61–67

21. Aravantinos G, Pectasides D (2014) Bevacizumab in combination with chemotherapy for the treatment of advanced ovarian cancer: a systematic review. J Ovarian Res 7:57

22. Burger RA, Brady MF, Bookman MA et al (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365(26):2473–2483

23. Komiyama S, Kato K, Inokuchi Y et al (2019) 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 24(1):103–114

24. Yoshida H, Yabuno A, Fujiwara K (2015) Critical appraisal of bevacizumab in the treatment of ovarian cancer. Drug Des Devel Ther 9:2351–2358

25. Pharmaceutical interview form: Doxil injection 20 mg (in Japanese). Japanese standard product classification number 874235. Revised January 2021 (third edition). Available at http://www.mochida.co.jp/dis/interview/dxl_n4.pdf. Accessed Feb 2021

26. Pharmaceutical interview form: Taxol injection 30 mg and 100 mg (in Japanese). Japanese standard product classification number 87424. Revised February 2018 (tenth edition). Available at http://file.bmshealthcare.jp/bmshealthcare/pdf/interview/IF_TX1802.pdf. Accessed Feb 2021

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