Hypertension and Proteinuria as Predictive Factors of Effects of Bevacizumab on Advanced Breast Cancer in Japan

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Bevacizumab (BV), an inhibitor of vascular endothelial growth factor, is used in combination with paclitaxel (PTX) to treat advanced breast cancer. Hypertension and proteinuria are characteristic adverse events of BV therapy. We assessed the potential of these adverse events as predictors of BV treatment responses. Our results revealed that groups that developed hypertension and proteinuria early (by day 56) had a stronger antitumor response (Fisher’s exact test *p<0.05). However, no significant difference was observed in progression-free survival (the Kaplan–Meier method and Log-rank test). As a reference, age, the treatment line, subtypes, liver and renal function, diabetes mellitus and hyperlipidemia history, body mass index, influencing concomitant medicine, average relative dose intensity and hematotoxicity did not significantly differ between groups with or without hypertension and with or without proteinuria. These results indicate the potential of the development of hypertension and proteinuria as predictors of improved outcomes with PTX plus BV therapy in patients with breast cancer. However, since both adverse events may preclude the continuation of treatment, their earlier management may be required.

Key words bevacizumab; advanced breast cancer; hypertension; proteinuria

Bevacizumab (BV), an inhibitor of vascular endothelial growth factor (VEGF), is used in combination with paclitaxel (PTX) to treat inoperable, advanced, or recurrent breast cancer (PTX 90 mg/m2 on days 1, 8, and 15, BV 10 mg/kg on days 1 and 15 of a 28-d cycle).1) Hypertension and proteinuria are characteristic adverse events of BV therapy, the incidence of which were reported to be 17.9 and 10.5%, respectively, in a clinical study.1) One proposed mechanism underlying BV-induced hypertension is BV inhibiting VEGF, which enhances endothelial nitric oxide synthase activity, resulting in the decreased production of the vasodilator nitric oxide.2)

The development of proteinuria has been attributed to VEGF, which has been suggested to play a role in the maintenance of glomerular microvascular endothelial cell function, being inhibited by BV, resulting in the disrupted recovery of glomerular capillaries. Therefore, glomerular filtration decreases, leading to protein leakage into urine.3) Experimental findings have also shown that glomerular injury may be due to reduced local VEGF production by glomerular podocytes.3)

Several phase III trials on BV combined with chemotherapy in first- and second-line treatments for metastatic and recurrent HER2-negative breast cancer have been published, and all showed improved response rates and progression-free survival (PFS), but not overall survival (OS).5-11) Therefore, when given in combination with standard therapy for metastatic and recurrent breast cancer, BV may improve PFS and response rates. However, the usefulness of BV for improving OS has not yet been confirmed, and the risk of BV-characteristic adverse events may increase. Prolonged PFS alone may not be of clinical benefit to patients; therefore, based on the absence of established predictive biomarkers for treatment effects, patients who receive BV need to be carefully selected. However, this drug may play a role in certain cases, including those requiring immediate responses.

VEGF-A has been reported as a useful marker for predicting the effects of BV12,13); the global double-blind randomized control study, MERiDiAN is ongoing to reexamine the efficacy of combination therapy with BV plus paclitaxel and investigate biomarkers of BV in patients stratified according to plasma VEGF-A levels.

Several retrospective studies have shown a relationship between hypertension and the therapeutic effects of BV in patients with colorectal cancer4,15); however, limited information is currently available on other cancer types. The E2100 study demonstrated a significant difference in therapeutic effects according to the genotypes of patients with breast cancer. To the best of our knowledge, the relationship between proteinuria and BV therapeutic effects has not yet been examined.

We performed a retrospective study on Japanese patients with breast cancer in order to investigate the potential of hypertension as a biomarker of BV therapy, as previously demonstrated in studies on other cancer types. We also assessed the relationships of proteinuria and other factors with BV therapy.

PATIENTS AND METHODS

Patients and Study Period Of 21 breast cancer patients who received BV for the first time in combination with PTX at Kagawa University Hospital between May 2012 and January 2016, 19 were included in this study. Two patients who received BV as part of neoadjuvant chemotherapy were excluded. The observation period was from the first dose to February 2017. This study was approved by the Kagawa University Ethical Research Committee (No. 27-007).

Study Items Age, treatment lines, subtypes, hypertension and proteinuria grades, liver dysfunction, renal function,
diabetes mellitus history, hyperlipidemia history, body mass index (BMI), hematotoxicity, response evaluations, influencing concomitant medicine, average relative dose intensity (ARDI) and PFS were retrospectively assessed by reviewing electronic medical records. Influencing concomitant medicines were extracted with hypertension, hypotension and proteinuria described in the package inserts. Antihypertensive medications against adverse event of BV were excluded as influencing concomitant medicines, because they were counted as assessment grade of hypertension.

**Adverse Event Criteria** Hypertension and proteinuria were assessed using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0). Patients were then grouped according to the presence (grade 1 or higher) or absence (no grade) of each adverse event. In order to assess the potential of these adverse events as predictors of treatment responses, the observation period was for 8 weeks starting from the initiation of treatment, i.e., until the end of the second course of anticancer therapy. Liver dysfunction and hematotoxicity were assessed using CTCAE v 4.0, and the aggravation of grade 1 or more for liver dysfunction (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (T-Bil)) and grade 2 or more for hematotoxicity (leukopenia, hemoglobin levels, platelet counts, neutropenia) were investigated. Renal function was compared using creatinine clearance calculated by the Cockcroft–Gault equation.

**Assessment of Treatment Effectiveness** Best antitumor responses during the treatment period were assessed with response evaluations (complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)) by physicians according to the Response Evaluation Criteria in Solid Tumors (RECIST). Between-group PFS comparisons were also performed.

**Statistical Analysis** We used SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, U.S.A.). Baseline patient characteristics were analyzed using the Mann–Whitney U-test and Fisher's exact test. We used Fisher’s exact test for between-group antitumor effect comparisons, with $p<0.05$ indicating a significant difference. The Kaplan–Meier method was used in the PFS analysis and the Log-rank test was employed for comparisons between groups, with $p<0.05$ indicating a significant difference.

**RESULTS**

**Baseline Characteristics of Hypertensive and Non-hypertensive Groups and Proteinuria and Non-proteinuria Groups** All 19 patients were females with advanced recurrent breast cancer. The median age was 56 years (range, 37 to 79). The median number of treatment lines was 5 (range, 1 to 11). Baseline patient characteristics for the groups are shown in Tables 1A and B. Age, the treatment line, subtypes, liver and renal function, diabetes mellitus and hyperlipidemia history, and BMI did not significantly differ between the hypertensive and non-hypertensive groups and the proteinuria and non-proteinuria groups.

**Antitumor Effect Comparisons for Hypertensive and Non-hypertensive Groups and Proteinuria and Non-proteinuria Groups** Antitumor effect comparison results between groups with and without hypertension and with and without proteinuria are shown in Tables 2A and B. While no patients achieved CR, all patients in the hypertensive and proteinuria groups had PR with an objective response (CR+PR) of 100%, a result that revealed a significantly stronger antitumor response in the two adverse event groups ($p<0.05$). No characteristic differences were observed in other adverse events, influencing medicine and ARDI between the two groups. Influencing medicines were pregabalin, celecoxib, fentanyl patch in hypertension or hypotension, and non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and proton pump inhibitors in proteinuria. The frequency of adverse event of either medicine was less than 1% or unknown.

**PFS Comparisons for Hypertensive and Non-hypertensive Groups and Proteinuria and Non-proteinuria Groups** Figures 1A and B show the results of PFS comparisons between the groups with and without hypertension and with and without proteinuria.

**Table 1. Baseline Characteristics of Patients with or without Hypertension and Proteinuria**

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive group</th>
<th>Non-hypertensive group</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>7</td>
<td>12</td>
<td>0.902(a)</td>
</tr>
<tr>
<td>(Range)</td>
<td>(37–73)</td>
<td>(45–79)</td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>56</td>
<td>59.5</td>
<td></td>
</tr>
<tr>
<td>(Range)</td>
<td>(37–79)</td>
<td>(45–75)</td>
<td></td>
</tr>
<tr>
<td>Median therapy line</td>
<td>3</td>
<td>5.5</td>
<td>0.227(a)</td>
</tr>
<tr>
<td>(Range)</td>
<td>(1–8)</td>
<td>(1–11)</td>
<td></td>
</tr>
<tr>
<td>Subtypes</td>
<td>Luminal A</td>
<td>2</td>
<td>0.505(b)</td>
</tr>
<tr>
<td></td>
<td>Luminal B (Her 2 −)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luminal B (Her 2 +)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Her 2 type</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triple negative</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver dysfunction</td>
<td>4</td>
<td>0.650(b)</td>
</tr>
<tr>
<td></td>
<td>Renal function (Mean±S.D.)</td>
<td>87.7±17.2</td>
<td>78.3±19.3</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1.000(b)</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>1</td>
<td>1.000(b)</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>23.2±3.5</td>
<td>22.6±3.2</td>
</tr>
</tbody>
</table>

\(a\) The Mann–Whitney U test. \(b\) Fisher’s exact test.
without proteinuria. The median PFS for patients with and without hypertension were 355 and 147 d, respectively. The median PFS for patients with and without proteinuria were 504 and 173 d, respectively. Patients with the adverse events of proteinuria and hypertension had slightly longer PFS.

DISCUSSION

While the emergence of molecular targeted drugs has clearly improved treatment outcomes in patients with cancer, characteristic adverse events, which were not previously observed with the use of conventional cytotoxic anticancer drugs, have been an issue. However, these characteristic adverse events may have potential as predictors of improved outcomes. One example is a rash caused by the use of an Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor and EGFR monoclonal antibodies, which has been reported as a possible predictor of treatment outcomes. The development of these adverse events in the initial period of treatment is associated with antitumor effects and has potential as a predictor of treatment effectiveness. However, it is necessary to re-assess PFS with a larger number of cases because slightly longer PFS was detected.

In the E2100 study on patients with breast cancer, a subgroup analysis stratified by genotype showed between-group differences in the therapeutic effects of BV as well as in OS. In addition, a difference in OS has been reported in patients with grade 3 or 4 hypertension. Our results indicate that even grade 1 hypertension, when occurring early within 8 weeks of the administration of the first dose, is associated with a difference in treatment effectiveness. Furthermore, the relationship between proteinuria and the therapeutic effects of BV has not yet been examined, the possibility of which is newly presented herein. Even grade 1 hypertension or proteinuria, when it occurs early, may be indicative of favorable outcomes for BV therapy. Since hypertension and proteinuria, which are considered to be interrelated with the pharmacological actions of BV, strongly correlated in our study (6 out of 7 patients developed these adverse events), difficulties are associated with identifying which of the two may be more useful as a predictive factor. Therefore, we consider the development of hypertension or proteinuria to be indicative of a greater likelihood of therapeutic efficacy.

If hypertension occurs, treatment may be continued with the concomitant use of appropriate antihypertensive medication. Additionally, grade 2 and higher proteinuria requires the discontinuation of BV; however, our results indicate that patients who developed adverse events early benefited from BV therapy, even after its discontinuation. Therefore, the early detection of adverse events and careful continuation of BV may result in improved outcomes.

Although an increase in the cumulative dose of BV may lead to an increased incidence of hypertension and proteinuria, this was not considered to markedly affect the results obtained herein because our 8-week observation period was shorter than the 60 d described in the study by Hurwitz et al. In
the present study, we targeted Japanese breast cancer patients treated with the same regimen; however, our results may lack reliability because the number of subjects was small. Therefore, further studies with a larger sample size are warranted.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) AVASTIN package insert, Chugai Pharmacy, Tokyo, Japan (May 2016).


