Deterioration of Glycemic Control Contributes to the Prevalence of Proteinuria among Bevacizumab-Treated Cancer Patients with Type 2 Diabetes Mellitus

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The objective of this study was to investigate whether improving glycemic control reduces the prevalence and progression of proteinuria among bevacizumab (BEV)-treated cancer patients with type 2 diabetes mellitus (DM). We retrospectively reviewed the medical records of 55 patients with type 2 DM who were treated with BEV between July 1 2011 and May 31 2018 at Iwate Medical University Hospital. The patients were classified based on changes in glycated hemoglobin (HbA1c) level during the 3 months following BEV administration into the “HbA1c elevated” group (+0.5% or above, n=24) and the “HbA1c non-elevated” group (indicating no change or decrease; n=31). At 3 months following BEV administration, the means of HbA1c and its change rate in the ‘HbA1c elevated’ group was significantly higher than that in the ‘HbA1c non-elevated’ group, and the prevalence of proteinuria in the ‘HbA1c elevated’ group was significantly higher than that in the ‘HbA1c non-elevated’ group. Additionally, our subjects were classified into the proteinuria group and non-proteinuria group. The mean HbA1c level in the proteinuria group was significantly higher than that in the non-proteinuria group at 3 months following BEV administration. Furthermore, the mean rates of change of HbA1c level in patients experiencing grades 1 and 2 proteinuria were +9.97±2.26 and +14.0±3.82%, respectively. These values were significantly higher than those of patients with no proteinuria (~2.15±1.96%). Our results suggest that deterioration of glycemic control contributes to the prevalence of proteinuria among BEV-treated cancer patients with type 2 DM.

Key words glycemic control; bevacizumab; proteinuria; type 2 diabetes; cancer patient

The molecularly targeted drug bevacizumab (BEV) is a recombinant humanized monoclonal antibody against the human vascular endothelial growth factor (VEGF). VEGF is one of the cytokines that promote angiogenesis by increasing the division rate of endothelial cells, and also functions as a survival factor.2) BEV binds specifically to VEGF and interferes with its biological activity, inhibiting angiogenesis in tumor tissue and exerting an antitumor effect.2) Additionally, BEV has been shown to be effective when used in combination with standard chemotherapy for patients with advanced or recurrent colorectal cancer in which curative resection is not possible, those with unresectable advanced or recurrent non-small-cell lung cancer (except squamous cell carcinoma), those with inoperable or recurrent breast cancer, and those with glioblastoma.3–6)

The typical adverse effects of BEV include hypertension, proteinuria, bleeding, and thrombophlebitis.7–9) In particular, the incidence of proteinuria among BEV-treated patients is reported to be 18–23%; most patients experience grades 1 or 2 proteinuria while grades 3 and 4 are rare.10,11) The development of proteinuria of grades ≥3 may cause renal failure as well as discontinuation of BEV administration10,11); therefore, it is important to monitor patients undergoing BEV treatment for the occurrence of proteinuria.

Several studies have shown that diabetes (DM), hypertension, prolonged BEV administration, and increased doses of BEV are risk factors for proteinuria in BEV-treated patients.12,13) Since the deterioration of glycemic control is closely associated with the onset of diabetic nephropathy, BEV-treated patients with DM should ostensibly maintain adequate glycemic control; however, no studies have investigated whether improvement in glycemic control reduces the incidence and progression of proteinuria in such patients.

Therefore, we conducted a retrospective survey of patients with DM who had received BEV combination chemotherapy. Additionally, we investigated the levels of hemoglobin A1c (HbA1c), a biomarker of glycemic control, in these patients and evaluated the association between HbA1c changes and progression of proteinuria.

PATIENTS AND METHODS

Patients Japanese adults with cancer who were outpatients at Iwate Medical University Hospital between July 1 2011 and May 31 2018, received first-time BEV treatment at doses of 5, 10, and 15 mg/kg for 3 months, and had type 2 DM were included in this study. Patients with metastatic pancreatic cancer, diabetic nephropathy, prior proteinuria, elevated blood pressure (≥150/90mmHg), liver and kidney dysfunction, or inadequate laboratory data at the start of BEV administration.
were excluded from the analysis. Additionally, patients whose BEV doses and chemotherapy regimens were changed, as well as those who switched the type and dose of their administered antihypertensive and antidiabetic drugs within 3 months of the start of BEV treatment, were also excluded. This study was reviewed and approved by the Iwate Medical University Ethics Committee (approval no. MH2018-029); no written informed consent was acquired owing to the retrospective nature of the study.

Retrospective Survey Data on sex, age, height, weight, type of cancer, BEV dose, presence of proteinuria, antitumor chemotherapy regimen agents, concomitant drugs (oral DM and antihypertensive agents), laboratory test results (including the levels of alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum creatinine [Scr], blood pressure [systolic and diastolic], and HbA1c) at initial BEV administration and 3 months thereafter were retrieved from medical records and examined. The estimated glomerular filtration rate (eGFR) was calculated using the sex, Scr, and age of each patient using the estimation equation proposed by the Japanese Society of Nephrology.14 Proteinuria was considered present if the urinary albumin dipstick test showed positive (≥1+) results. The progression of proteinuria was evaluated according to the Common Terminology Criteria for Adverse Events version 4.0, which were modified by the Japan Clinical Oncology Group15 in which proteinuria scores of 1+ and 2+/3+ were considered as grades 1 and 2, respectively.

Analysis of the Association between Progression of Proteinuria and Change in HbA1c Level We classified patients who experienced a +0.5% or greater change in HbA1c level over 3 months following initial BEV administration into the “HbA1c elevated” group, whereas those with a change in HbA1c level lower than +0.5% over the same period (including decreases) were classified as the “HbA1c non-elevated” group. The prevalence of proteinuria, BEV dose, cumulative BEV dose, and laboratory data between the 2 groups were compared.

In addition, we classified the same patients into the “proteinuria group” or “non-proteinuria group based on the occurrence of proteinuria at 3 months following BEV administration. BEV dose, cumulative BEV dose, and laboratory data between the 2 groups were compared, and the association between the prevalence of proteinuria and change in HbA1c level were analyzed.

Statistical Analysis The 2 groups were compared using the chi-squared test, Student’s t-test, or Mann–Whitney U-test. The relationship between HbA1c change and incidence of proteinuria was analyzed using the chi-squared test. The mean rates of change in HbA1c level were analyzed using the Steel–Dwass test. Differences were considered statistically significant if their p-values were <0.05. Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, U.S.A.).

RESULTS AND DISCUSSION

Patients Seventy-one patients were identified and reviewed in this study. Five of these patients experienced an onset of proteinuria upon first commencing BEV administration, 7 had elevated blood pressure (≥150/90 mmHg), and 4 experienced changes in their doses of diabetic and antihypertensive agents; these 16 patients were therefore excluded from the analysis. Finally, the data of 55 patients were analyzed in this study.

Characteristics of Patients Classified into the HbA1c Elevated and Non-elevated Groups Of the remaining 55 patients, 24 were classified into the ‘HbA1c elevated’ group and the remaining 31 patients were classified into the ‘HbA1c non-elevated’ group.

At the time of commencing BEV administration, the sex ratio, age, body mass index, BEV dose, usage of antidiabetic and antihypertensive agents, implementation status of chemotherapy, and ALT, AST, Scr, blood pressure, eGFR, and HbA1c were not significantly different between the 2 groups (Table 1). At 3 months after BEV administration, there remained no significant difference in AST, ALT, Scr, eGFR, blood pressure, and cumulative BEV dose between the 2 groups (Table 2). However, the mean HbA1c level and its change rate in the ‘HbA1c elevated’ group were significantly higher than those in the ‘HbA1c non-elevated’ group. Additionally, the prevalence of proteinuria in the ‘HbA1c elevated’ group was significantly higher than that in the ‘HbA1c non-elevated’ group. This observation suggests that the change in HbA1c level was significantly related to the onset of proteinuria in BEV-treated patients with type 2 DM (Table 2).

Characteristics of Patients Classified into the Proteinuria and Non-proteinuria Groups Of 55 patients, 20 were classified into the proteinuria group and the remaining 35 patients were classified into the non-proteinuria group. At the time of commencing BEV administration, the sex ratio, age, body mass index, BEV dose, use of antidiabetic and antihypertensive agents, implementation status of chemotherapy, and ALT, AST, Scr, blood pressure, eGFR, and HbA1c were not significantly different between the two groups (Table 3). At 3 months after BEV administration, there remained no significant difference in AST, ALT, Scr, eGFR, blood pressure, and cumulative BEV dose between the two groups (Table 4). However, the mean HbA1c level in the proteinuria group was significantly higher than that in the non-proteinuria group. This observation suggests that the increase in HbA1c level might be related to the prevalence of proteinuria among BEV-treated patients with type 2 DM (Table 4).

The Relationship between Changes in HbA1c Level and Progression of Proteinuria To investigate whether the progression of proteinuria was associated with the increase in HbA1c level, the relationship between the rate of change in HbA1c level and degree of proteinuria was analyzed. The mean rates of change in HbA1c level in patients experiencing grades 1 and 2 proteinuria tended to be higher than in those with grade 1 proteinuria (p = 0.623), suggesting an association between an increase in HbA1c level and the progression of proteinuria. This implies that improving glycemic control might reduce the prevalence and progression of proteinuria among BEV-treated cancer patients with type 2 DM.

Proteinuria is closely associated with the disintegration of the glomerular filtration barrier.16 In this study, the mean eGFR, an index of renal glomerular function, in patients with
Furthermore, sustained hyperglycemia was shown to increase angiotensin II receptor blocker; CCB: calcium channel blocker; *TMZ: temozolomide; co-transporter-2 inhibitors; ACE-I: angiotensin-converting enzyme inhibitor; ARB: dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitor: sodium-glucose co-transporter; BMI: body mass index; Scr: serum creatinine; eGFR: estimated glomerular filtration rate calculated based on age, Scr, and sex. The laboratory data are presented as mean ± standard error. 0.5% 0.01 0.01 0.01

| Table 1. Comparison of Patient Characteristics in the HbA1c Elevated and Non-elevated Groups at the Onset of Bevacizumab Treatment |
|-----------------|----------------|----------------|----------------|
|                  | Non-elevated  | Elevated       | p-Value        |
|                  | <0.5% (n=31)  | ≥0.5% (n=24)   |                |
| **Sex (male/female)** | 16/15        | 15/9           | 0.419<sup>a</sup> |
| **Age (years)**   | 64.9±1.48    | 64.8±1.89      | 0.964<sup>b</sup> |
| **BMI**          | 23.7±0.68    | 22.9±1.12      | 0.484<sup>b</sup> |
| **AST (IU/L)**    | 22.6±1.66    | 25.3±2.92      | 0.406<sup>b</sup> |
| **ALT (IU/L)**    | 24.1±2.46    | 22.9±2.50      | 0.777<sup>b</sup> |
| **Scr (mg/dL)**   | 0.69±0.03    | 0.73±0.03      | 0.376<sup>b</sup> |
| eGFR (mL/min/1.73 m²) | 80.3±3.31   | 79.1±3.48      | 0.813<sup>b</sup> |
| **Blood pressure** |              |                |                |
| Systolic (mmHg)  | 128.5±2.17   | 131.1±3.19     | 0.477<sup>b</sup> |
| Diastolic (mmHg) | 74.7±1.49    | 77.2±2.18      | 0.333<sup>b</sup> |
| HbA1c (%)        | 6.88±0.13    | 7.18±0.18      | 0.494<sup>b</sup> |
| BEV dose (mg/body) | 523.3±48.7  | 474.2±54.3     | 0.505<sup>b</sup> |
| **Chemotherapy regimen** |         |                |                |
| TMZ             | 2            | 3              | 0.957<sup>b</sup> |
| CDDP + PEM      | 2            | 2              |                |
| TC              | 8            | 5              |                |
| FOLFOSX6        | 12           | 10             |                |
| FOLFIRI         | 3            | 2              |                |
| PTX             | 4            | 2              |                |
| **Type of cancer** |              |                |                |
| Colon           | 16           | 12             | 0.844<sup>c</sup> |
| Ovary           | 5            | 5              |                |
| Lung            | 5            | 3              |                |
| Breast          | 3            | 1              |                |
| Glioblastoma    | 2            | 3              |                |
| **Diabetes agents** |            |                |                |
| Sulfonylurea    | 1            | 1              | 0.955<sup>c</sup> |
| α-GIs           | 7            | 4              |                |
| DPP-4 inhibitors | 13           | 18             |                |
| SGLT2 inhibitors | 2            | 2              |                |
| Biguanide       | 1            | 2              |                |
| Pioglitazone    | 1            | 1              |                |
| Insulin         | 8            | 8              |                |
| No medication   | 2            | 1              |                |
| **Antihypertensive agents** |      |                |                |
| ACE-I/ARB       | 8            | 7              | 0.818<sup>c</sup> |
| CCB             | 10           | 8              |                |
| Diuretics       | 2            | 4              |                |
| No medication   | 1            | 1              |                |

HbA1c: glycated hemoglobin; AST: aspartate transferase; ALT: alanine aminotransferase; BMI: body mass index; Scr: serum creatinine; eGFR: estimated glomerular filtration rate calculated based on age, sex, and Scr. The laboratory data are presented as mean±standard error. a) Student’s t-test; b) Mann–Whitney U-test; c) Chi-square test, *p<0.05.

and without proteinuria were found not to be significantly different (Table 4), indicating that proteinuria in BEV-treated patients with type 2 DM did not necessarily lead to a decrease in eGFR. Hayman et al. reported that the onset of proteinuria caused by BEV treatment is related to podocyte loss.<sup>27</sup> Furthermore, sustained hyperglycemia was shown to increase the permeability of the glomerular filtration barrier through podocyte foot process effacement, leading to proteinuria.<sup>18</sup> These findings suggest that DM is a risk factor for proteinuria through podocyte depletion in BEV-treated patients; however, podocyte foot process effacement is not correlated with proteinuria in human glomerulopathies.<sup>19</sup> A recent study using human podocytes obtained from patients with Alport syndrome reported that proteinuria was an early event that occurred at approximately 25% podocyte depletion, although the eGFR did not change until >70% podocyte depletion,<sup>20</sup> indicating that proteinuria precedes the decrease in eGFR. Additionally, the same study revealed that patients with proteinuria might exhibit the onset of podocyte depletion despite the lack of decrease in eGFR. As such, patients in the ‘HbA1c elevated’ groups in our study may have had increased podocyte depletion compared to those in the ‘HbA1c non-elevated’ group, which may have resulted in the positive relationship between elevated HbA1c and the progression of proteinuria observed in our study.

The objective of our study was to investigate whether changes in HbA1c level were associated with progression of proteinuria in BEV-treated patients with type 2 DM. To evaluate this relationship properly, we excluded subjects who expressed risk factors such as elevated blood pressure, diabetic nephropathy, pancreatic cancer metastasis, and changes in BEV administration dose and duration. Since BEV treatment is considered a last-line cancer therapy, its discontinuation due to proteinuria progression can be detrimental to patients affected with surgically unresectable cancers. Our observations show that glycemic control is important for the prevention of progression of proteinuria in BEV-treated patients with DM, which has critical implications for patients with cancer as well as their treatment.

This study had several limitations. It was a small retrospective investigation conducted at a single center, and the preva-
ence and progression of proteinuria were evaluated using the simple urine dipstick method. Evaluating the spot urine albumin-to-creatinine ratio might provide a better assessment of proteinuria than the simple urine dipstick measurement. Therefore, our findings require validation in a prospective study in which proteinuria and renal function are evaluated with greater reliability and precision. In addition, HbA1c value is considered to insufficiently reflect glycemic control. Measurement of the value of glycoalbumin, reflecting the mean blood glucose level over 2 weeks, might be suitable for evaluation of change in glycemic control in 3 months.

In conclusion, our data suggest that the increase in HbA1c level is related to the prevalence and progression of proteinuria in BEV-treated cancer patients with type 2 DM. Our results ought to provide useful information to healthcare professionals involved in the administration of BEV treatment.

Conflict of Interest  The authors declare no conflict of interest.

REFERENCES

1) Ferrara N. Vascular endothelial growth factor. Arterioscler. Thromb.
Bevacizumab significantly increases the risks of hypertension and proteinuria in cancer patients: A systematic review and comprehensive meta-analysis. Oncotarget, 8, 51492–51506 (2017).

Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, Schulz J, Richards D, Soufi-Mahjoubi R, Wang B, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J. Clin. Oncol., 25, 4779–4786 (2007).

Leventhal RS, Koski S, Lichtenmayer M, Diaz-Yang R, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J. Clin. Oncol., 26, 2013–2019 (2008).

Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Lai XX, Xu RA, Yu-Ping L, Yang H. Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung tumors and other disorders. Cancer Res., 75, 891–898 (2015).

Fonseca MA, Smit EF, Lorigan P, Konduri K, Reck M, Szczesna A, Blakely J, Serwatowski P, Karaseva NA, Ciuleanu I, Jäsmen J, Dediu M, Hong S, Visseren-Gruul C, Hanuske AR, Obasaju CK, Guba SC, Thatcher N. Phase III study of pemetrexed plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer. J. Clin. Oncol., 27, 4787–4792 (2009).

Botrel TEA, Clark LG, Paladini L, Clark OAC. Efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated advanced or metastatic colorectal cancer: a systematic review and meta-analysis. BMC Cancer, 16, 677 (2016).

Isobe T, Uchino K, Makiyama C, Ariyama H, Arita S, Tamura S, Komoda M, Kusaba H, Shirakawa T, Esaki T, Mitsugi K, Takeishi S, Akashi K, Baba E. Analysis of adverse events of bevacizumab-containing systemic chemotherapy for metastatic colorectal cancer in Japan. Anticancer Res., 34, 2035–2040 (2014).

Lai XX, Xu RA, Yu-Ping L, Yang H. Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Onco Targets Ther., 9, 2421–2428 (2016).

Zhao T, Wang X, Xu T, Xu X, Liu Z. Bevacizumab significantly in-