Analysis of Adverse Events of Bevacizumab-containing Systemic Chemotherapy for Metastatic Colorectal Cancer in Japan

TAICHI ISOBE[1], KEITA UCHINO[2], CHINATSU MAKIYAMA[1], HIROSHI ARIYAMA[1], SHUJI ARITA[1,6], SHINGO TAMURA[1], MASATO KOMODA[2], HITOSHI KUSABA[1], TSUYOSHI SHIRAKAWA[3], TAITO ESAKI[3], KENJI MITSUGI[4], SHIGEO TAKAISHI[5], KOICHI AKASHI[1] and EISHI BABA[6]

[1]*Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan;*
[2]*Department of Medical Oncology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;*
[3]*Department of Gastroenterology and Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan*
[4]*Department of Oncology, Hamanomachi Hospital, Fukuoka, Japan;*
[5]*Center for Advanced Medical Innovation, Kyushu University, Fukuoka, Japan;*
[6]*Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan*

Abstract. *Background: Bevacizumab (BV) is widely used in chemotherapy for metastatic colorectal cancer (mCRC). Although specific adverse events have been observed, their risk factors have not been clarified. Patients and Methods: 178 mCRC patients who underwent chemotherapy were retrospectively examined and correlations between possible risk factors and adverse events were analyzed. Results: 87 out of 178 patients were treated with BV-containing chemotherapy. Possible risk factors for BV-related adverse events were: remaining primary tumor, current bleeding, history of arterial thromboembolism (ATE), hypertension, and proteinuria, and these were observed in 22%, 2%, 7%, 16%, and 8% of patients, respectively. Patients with hypertension prior to chemotherapy developed significantly worse hypertension (p=0.018). Gastrointestinal bleeding occurred in 3 out of 18 patients with residual primary tumor (16.7%) and 6 out of 63 patients with no primary tumor (8.7%) (p=0.385). Conclusion: Pre-existing hypertension appears to be a risk factor for BV-related deterioration of hypertension.*

Correspondence to: Eishi Baba, MD, Ph.D, Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 Japan. Tel: +81 926426921, Fax: +81 926426922, e-mail: e-baba@c-oncology.med.kyushu-u.ac.jp

Kew Words: Colorectal cancer, chemotherapy, bevacizumab, adverse events.

Systemic chemotherapy has been developed as a standard therapy against metastatic colorectal cancer (mCRC), and therapeutic outcomes have since improved. In addition to cytotoxic agents, inhibition of vascular endothelial growth factor (VEGF) has been one of the key strategies for several types of solid tumors whose growth depends on neovascularization (1). VEGF is a glycoprotein physiologically-regulating vascular permeability and neovascularization. Moreover, tumor cells often produce large amounts of VEGF and depend on VEGF-induced neovascularization supplying oxygen and nutrition.

Bevacizumab (BV) is a recombinant, humanized, monoclonal antibody against human VEGF-A that inhibits the binding of VEGF-A to VEGFR and subsequent growth of endothelial cells. It has also been reported that normalization of abnormal tumor vasculature by BV contributes to maintaining interstitial pressure of tumor tissue and effectively delivering drugs to the tumor cells (2-4). BV has been well-investigated for its therapeutic effects on mCRC in clinical trials (5-8). In combination with fluorouracil-based regimens, BV has been reported to provide longer progression-free survival and overall survival in large-scale, randomized, clinical trials (5-7). Based on these results, BV was approved for the first-line and second-line treatment of mCRC in the United States in 2004 and in Japan in 2007.

Although BV shows remarkable clinical benefits, specific adverse events including not only frequently-observed proteinuria and hypertension, but also more serious conditions including gastrointestinal (GI) perforation, bleeding, and arterial thromboembolism (ATE), have been

reported (5-7). Thus, the risks for the occurrence of adverse events should be assessed. BRiTE, a prospective, observational cohort study of BV-based chemotherapy for mCRC, showed the possible risk factors for GI perforation and ATE: age above 65 years, intact primary tumors, and prior adjuvant radiotherapy were related to GI perforation, and performance status greater than 1, hypertension, and past history of arterial disease were related to ATE (9).

Little information regarding the effects and adverse events of BV-containing chemotherapies in Japanese mCRC patients is available, because few prospective, large-scale, clinical studies using BV-containing regimens for mCRC have been performed in Japan. Therefore, predictive factors of BV-related adverse events and precise guidelines for administration of BV to Japanese mCRC patients are not well-established. In order to clarify the relationship between predictive factors and adverse events of BV-containing chemotherapy in Japanese patients, patients' background characteristics and frequencies of adverse events with systemic chemotherapy for mCRC were retrospectively investigated.

Patients and Methods

Patients. The present study retrospectively investigated 178 patients with unresectable, recurrent, or metastatic colorectal adenocarcinoma who started systemic chemotherapy during the period from June 11, 2007 to August 31, 2008 in three Institutions: the Department of Hematology and Oncology of Kyushu University Hospital, the Gastrointestinal and Medical Oncology Division of National Kyushu Cancer Center, and the Department of Medical Oncology in Hamanomachi Hospital, Fukuoka, Japan. Patients who were administered BV prior to this period were excluded.

Information of all cases was obtained from the participating Hospitals' medical records. Patients' background characteristics included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary site of the tumor, and possible risk factors for serious adverse events of BV including remaining primary tumor, current bleeding, past and present history of arterial thromboembolism (ATE), hypertension, and proteinuria. In patients who were treated with BV-containing regimens during this survey period (BV group), chemotherapy regimens and their duration, best therapeutic effects, adverse events, and reasons for withdrawal of BV administration were investigated. In patients who were treated with chemotherapy without BV (CT group), the reasons for the primary decision to not use BV-containing regimens when chemotherapy was started were examined. Adverse events that occurred in the CT group were also observed in the above period. The present study was carried out according to the regulations of local Ethics committee in each Hospital and the Declaration of Helsinki.

Treatment. Patients received fluoropyrimidine-based chemotherapy with or without BV until disease progression, occurrence of intolerable adverse events, or patient's refusal. The combined chemotherapy regimens were selected by the physicians with the patients' consent. The dose of BV was 5 mg/kg or 10 mg/kg every 2 weeks. BV was administered intravenously in 100 ml of saline for 30-90 min. In cases of adverse events, the BV dose was not reduced, but administration of BV was suspended until recovery from the adverse events.

Assessments. At every bi-weekly visit, patients were assessed for adverse events by physical examination, urinalysis, blood cell counts, and serum chemistry. All adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 3.0. The most severe grades of adverse events during chemotherapy were recorded.

Statistics. Analyses of correlations between the occurrence of BV-specific adverse events and their possible risk factors were performed using the Fisher's exact test.

Results

Patients' background characteristics and treatments. Overall, 87 of 178 patients were treated with BV-containing chemotherapy (BV group) during the observation period, and 91 patients were treated with non-BV-containing chemotherapy (CT group). No significant differences in sex, age, and primary site were identified between the two groups (Table I). Patients who had primary tumors tended to be treated with chemotherapy without BV. Bleeding risks were significantly more frequently observed in the CT group. No significant differences between the two patient groups were observed in the other factors.

In the BV group, BV-containing regimens were used in the first (17%), second (35%), and third line (29%) of chemotherapy (Table II). Combined chemotherapy regimens were oxaliplatin-based FOLFOX (48%) and irinotecan-based FOLFIRI or IFL (44%). The median number of BV administrations was 7, and the median duration of BV-containing chemotherapy was 8.1 months. In 71 regimens of BV-containing chemotherapy in which the therapeutic effect was confirmed until August 31, 2008, the response rate and the disease control rate were 18% and 78% in all lines of treatment, respectively, and 27% and 82% in first-line treatment, respectively (Table III). There were 15 patients who were treated with two BV-containing chemotherapy regimens. In 10 of these 15 patients, BV was administered after disease progression in their prior chemotherapy with BV. The other 5 patients stopped chemotherapy because of oxaliplatin-induced allergies (3 patients), diarrhea (1 patient), and patient's refusal (1 patient), but BV was continued for the subsequent chemotherapies including irinotecan-based or oxaliplatin-based regimens, which were not used in the prior therapy. The confirmed responses of the second BV-containing chemotherapy in 5 patients were 3 stable diseases and 2 progressive diseases.

Safety. Therapy-related toxicities in the BV group were assessed according to the Common Terminology Criteria of Adverse Events version 3.0 (CTC-AE ver.3.0) (Table IV). In

Table I. *Baseline characteristics of all patients.*

	BV-containing Regimen (BV group)		Non-BV-containing regimen (CT group)		
Characteristic	No.	%	No.	%	*p*-Value
Gender					
Male	47	54	44	48	0.45
Female	40	46	47	52	
Age					
Median (range), year	63 (36-82)		65 (21-84)		0.76
74 and younger	76	86	74	81	0.31
75 and older	11	14	17	19	
Primary tumor					
Colon	45	52	51	56	0.65
Rectum	42	48	40	44	
Resected	69	78	60	66	0.06
Remaining	18	22	31	34	
Bleeding risk					
None	85	98	75	82	< 0.01
Any risk	2	2	16	18	
Primary tumor	0		9		
Invading tumor	1		3		
Genital organ	1		2		
Surgical wound	0		1		
Thrombocytopenia	0		1		
Thromboembolic risk					
None	81	93	79	87	0.22
Any risk	6	7	11	13	
Cerebral infarction	4		4		
ASO	1		2		
Ischemic heart disease	1		1		
Severe Arteriosclerosis	0		2		
Atrial fibrillation	0		1		
DIC	0		1		
Blood pressure					
Normotension	73	84	70	77	0.26
Hypertension	14	16	21	23	
Proteinuria					
Negative	80	92	82	90	0.80
Positive	7	8	9	10	

BV; Bevacizumab, ASO; arteriosclerosis obliterans, DIC; disseminated intravascular coagulation.

Table II. *Characteristics of the systemic chemotherapy regimens of the BV group.*

Characteristics	Number of patients	%
Regimen	102	(Total)
FOLFOX	49	48
FOLFIRI/IFL	45	44
S-1 + Irinotecan	4	4
5-FU + LV	4	4
Administration of BV		
median (range)	7	(1-28)
Treatment with BV		
Continuation	48	55
Cessation	39	45
Duration of therapy		
median in months (range)	8.1	(0.5-14.0)
Treatment line		
1st	17	17
2nd	36	35
3rd	30	29
4th or later	19	19

FOLFOX; 5-FU/leucovorin plus oxaliplatin, FOLFIRI/IFL; 5-FU/leucovorin plus irinotecan, LV; leucovorin.

Table III. *Efficacy of chemotherapy in the BV group.*

	Response						
Treatment line	CR	PR	SD	PD	NE	RR (%)	DCR (%)
1st	0	3	6	1	1	27	82
2nd	0	5	14	5	1	20	76
3rd	0	4	14	6	0	17	75
4th or later	0	1	10	2	0	8	85
All	0	13	44	14	2	18	78

RR; Response rate, DCR; disease control rate.

terms of hematological toxicities, neutropenia was observed in 87% of patients (grade 3/4; 41%), anemia in 79% (grade 3/4; 5%) and thrombocytopenia in 17% (grade 3/4; 2%). Febrile neutropenia occurred in 8%. Concerning non-hematological toxicities, general fatigue was observed in 71%, anorexia in 76%, nausea and vomiting in 61%, and peripheral neuropathy in 64%. All grades of diarrhea occurred in 54% of patients, and more than grade 3 was seen in 5%. In BV-related toxicities, bleeding was observed in 23% of patients (10 cases of nasal bleeding, 1 case of gingival bleeding, 9 cases of gastrointestinal bleeding), hypertension in 22%, proteinuria in 15%, and delayed wound healing in 4%. There were no treatment-related deaths.

Risk factors for BV-related adverse events. The relationships between BV-related adverse events and possible risk factors were analyzed. Gastrointestinal perforation did not occur in patients with or without primary tumor lesions. As mentioned above, 9 patients had gastrointestinal bleeding, including 4 with melena, 4 with bleeding from the stoma, and 1 proctorrhagia, and no correlation was observed between remaining primary tumors and bleeding (Table V). No arterial thrombosis events occurred in the patients with or without a present or past history of thrombotic events. On the other hand, patients with hypertension before starting

Table IV. *Adverse events in the BV group.*

Adverse event	Grade (CTC-AE ver 3.0) 1	2	3	4	Total (%)	Grade 3/4 (%)
Neutropenia	22	18	24	12	87	41
Anemia	44	21	4	0	79	5
Thrombocytopenia	9	4	1	1	17	2
Febrile Neutropenia	-	-	6	1	8	8
Fatigue	42	19	1	0	71	1
Anorexia	46	19	1	0	76	1
Nausea/vomiting	42	10	1	0	61	1
Stomatitis	14	3	2	0	22	2
Diarrhea	35	8	3	1	54	5
Stomach ache	11	1	1	0	15	1
Peripheral neuropathy	31	18	7	0	64	8
Allergy	5	3	1	0	10	1
Nasal/gingival bleeding	11	0	0	0	11	0

Table V. *BV-containing regimen-related gastrointestinal bleeding in patients with or without primary tumor.*

Primary tumor	Gastrointestinal bleedings		
	No	Yes*	*p*-Value
Resected	63	6	0.39
Remained	15	3	

*These 9 cases with gastrointestinal bleedings include 4 melenas, 4 bleedings of stoma and 1 proctorrhagia.

BV-containing chemotherapy had significant deterioration of hypertension (p=0.02) (Table VI). Therapy-related deterioration of proteinuria was not correlated with presence of proteinuria before chemotherapy (Table VII).

Forty-eight patients in the BV group continued to the end of this surveillance period in August 2008, and 39 patients had stopped BV-containing chemotherapy because of progressive disease (20 patients) and toxicity (11 patients).

Reasons for non-BV chemotherapy in the CT group. The reasons why BV was not administered in the CT group were also determined (Table VIII). The most frequent reason for this was the risk of bleeding (11 patients, 12%); in detail, 5 patients in the CT group had active bleeding from the primary site, 3 had bleeding from sites of tumor invasion, and 2 had bleeding from invasion of genital organs and other sites. Eleven patients (12%) were not administered BV because due to patients' refusal. BV was not used in 10 patients with a current or past history of arterial thrombotic events and in 8 patients with severe peritoneal dissemination.

Table VI. *BV-containing regimen-related hypertension in patients with or without hypertension before therapy.*

Blood pressure before therapy	BP grade (CTC-AE v3.0) 0	1	2	3	4	*p*-Value
Normotension	60	8	5	0	0	0.02
Hypertension	8	1	4	1	0	

Since 7 patients had surgery immediately prior to chemotherapy, the use of BV was reduced.

Discussion

BV has been widely used in systemic chemotherapy for mCRC. Various large-scale, phase III clinical studies, mainly conducted in Western countries, have shown the efficacy and safety profiles of BV-containing chemotherapy regimens (5-8). Tamiya *et al*. (10) reported on a retrospective review of adverse events in 65 Japanese patients with mCRC treated with BV-containing regimens and showed similar safety profiles to those of previous prospective trials. Although these reports encouraged the use of BV as one of the standard chemotherapeutic agents for mCRC, selection of patients who could be safely treated with BV-containing therapy is required in the clinical setting. It is, thus, important to identify the risk factors for predicting adverse events specifically caused by BV in Japanese patients.

The present study analyzed clinical data from patients with mCRC who had been treated with systemic chemotherapy during the period of 15 months from the approval of BV in Japan. The efficacy and safety of BV-containing chemotherapies and the possible risk factors related to BV-specific adverse events were identified. Since it had been known that bleeding occurred in around 3% of patients with BV-containing chemotherapies (5-8), mCRC patients with possible bleeding risks were excluded from BV administration in the CT group. Two patients, one with a history of hemorrhage from a gynecological organ and another with a remaining primary tumor, were treated with a BV-containing regimen and had no bleeding episodes during the treatment period. The significant risk factors for bleeding could not be identified because no hemorrhagic events occurred in either the BV group or the CT group. These facts suggested that active bleeding or highly hemorrhagic lesions might be appropriate risk factors for BV-related severe bleeding, and avoidance of BV administration in this population might be appropriate. It may be important to assess the bleeding risk in advance to prevent severe bleeding, and BV might be administered safely to patients with a low bleeding risk.

Table VII. *BV-containing regimen-related deterioration of proteinuria in patients with proteinuria before therapy.*

Proteinuria before therapy (CTC-AE v3.0)	Proteinuria grade (Number of patients)					Deterioration (Number of patients)		*p*-Value
	0	1	2	3	4	No	Yes	
0	73	6	1	0	0	73	7	0.15
1	1	2	2	0	0	3	2	
2	0	0	2	0	0	2	0	

The incidence of arterial thrombosis has been reported to be 1.7% in a cytotoxic chemotherapy-alone group and 3.8% in a BV-containing chemotherapy group, in a meta-analysis including clinical trials for mCRC, non-small cell lung cancer, and breast cancer (11). The multivariate analysis revealed that age over 65 years (p=0.01) and a history of arterial thrombosis (p<0.001) were independent risk factors for ATE (11). In the present study, BV was not given to 10 patients with any risk of thrombosis. Given the risk factors demonstrated in the previous report, 339 cases were >65 years of age, and 89 cases had a history of thrombosis. In contrast, 6 patients who had had possible risks for thrombosis, such as a history of brain infarction in 4 patients, arteriosclerosis obliterans in 1, and ischemic heart disease in 1, were successfully treated in the present study. Importantly, the disease activities of thrombosis in all 6 patients were diagnosed as minimal prior to chemotherapy, and no severe thrombotic events occurred in these patients. Establishment of precise criteria for administering BV in patients with a history of thrombotic events is also required.

In the present study, hypertension prior to BV-containing therapy was identified as a significant risk factor for the induction of worse hypertension by BV. On the other hand, in the BRiTE study, *de novo* hypertension appeared in 22% of BV-treated patients without baseline hypertension, and deterioration of hypertension in BV-treated patients with baseline hypertension was similarly observed in 22% (9). Ethnic differences might explain for the difference between present findings and those of the previous study. It has been reported that the sensitivity to sodium differs between Asians and Caucasians or Africans, suggesting that molecular mechanisms of BV-induced hypertension may differ among races (12).

Identification of risk factors has two roles: prevention of severe toxicities induced by chemotherapy, and avoidance of losing the chance for patients to be treated with appropriate chemotherapy. Because patients harboring possible risks were often excluded from enrollment in clinical trials, prospective trials focusing on that population might be important. In addition, retrospective analysis might be helpful to reveal the safety and effectiveness of BV in such patient populations. The present study demonstrated that BV-containing therapy in Japanese mCRC patients showed a similar toxicity profile to the one previously reported. It was suggested that suitable assessment of possible risk factors could lead to safe treatment with BV. Since Japanese mCRC patients with hypertension had a higher possibility of worse hypertension with BV, careful follow-up is needed.

Table VIII. *Reasons for choosing non-BV chemotherapy.*

Reason	No.	%
Remained primary site	4	4
Bleeding risk at	11	12
Primary site	5	
Invaded site of tumor	3	
Genital organs	2	
Thrombocytopenia	1	
Thromboembolic risk	10	11
Cerebral infarction	4	
Severe arteriosclerosis	2	
Atrial fibrillation	1	
Ischemic heart disease	1	
Thrombocytosis	1	
DIC*	1	
Hypertension	1	1
Patient's refusal	11	12
Severe peritoneal dissemination	8	9
Immediately prior to operation	7	8
Doctor's decision	7	8
Poor performance status	5	5
Advanced age	4	4
Combined radiotherapy	3	3
Preceding operation	2	2
Changing hospital	1	1
Others	8	9
Double cancers	2	
Diabetes mellitus	2	
Aftereffect of prior therapy	2	
Neuroendcrine component	1	
Renal dysfunction	1	

*Disseminated intravascular coagulation.

Acknowledgements

The Authors would like to thank Dr. Risa Tanaka for providing patient data. The Authors would also like to thank the medical staff of each institution who contributed to treatment of the patients.

References

1 Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M and Ferrara N: Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res *57*: 4593-4599, 1997.

2 McCrudden KW, Hopkins B, Frischer J, Novikov A, Huang J, Kadenhe A, New T, Yokoi A, Yamashiro DJ, Kandel JJ and Middlesworth W: Anti-VEGF antibody in experimental hepatoblastoma: suppression of tumor growth and altered angiogenesis. J Pediatr Surg *38*: 308-314, 2003.

3 Yuan F, Chen Y, Dellian M, Safabakhsh N, Ferrara N and Jain RK: Time-dependent vascular regression and permeability changes in established human tumor xenografts induced by an anti-vascular endothelial growth factor/vascular permeability factor antibody. Proc Natl Acad Sci USA *93*: 14765-14770, 1996.

4 Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY and Jain RK: Direct evidence that the VEGF-specific antibody BV has antivascular effects in human rectal cancer. Nat Med *10*: 145-147, 2004.

5 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: BV plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350*: 2335-2342, 2004.

6 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Cassidy J: BV 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.

7 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB 3rd and Eastern Cooperative Oncology Group Study E3200: BV in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol *25*: 1539-1544, 2007.

8 Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, von Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S, on behalf of the ML18147 Study Investigators: Continuation of BV after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol *14*: 29-37, 2013.

9 Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinavar FF, Purdie DM, Ashby MA, Dong W, Sugrue MM, Grothey A; Investigators of the BRiTE study: Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist *14*: 862-870, 2009.

10 Tamiya A, Yamazaki K, Boku N, Machida N, Kojima T, Taku K, Yasui H, Fukutomi A, Hironaka S and Onozawa Y: Safety of BV treatment in combination with standard chemotherapy for metastatic colorectal cancer: a retrospective review of 65 Japanese patients. Int J Clin Oncol *14*: 513-517, 2009.

11 Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, Bergsland E, Ngai J, Holmgren E, Wang J and Hurwitz H: Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and BV. J Natl Cancer Inst *99*: 1232-1239, 2007.

12 International Consortium for Blood Pressure Genome-Wide Association Studies: Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature *478*: 103-109, 2011.

Received January 5, 2014
Revised January 15, 2014
Accepted January 17, 2014