Cancer, hypertension and risk for cardiovascular disease

Tomoyuki Kawada

I read the article by Liu *et al.* [1], who evaluated the risk of cardiovascular disease (CVD) among cancer patients following the use of the vascular endothelial growth factor (VEGF) signalling inhibitors. There is an increased risk of CVD among cancer patients with hypertension, and the prevalence of hypertension in renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, lung cancer and thyroid cancer patients were 33.5, 29.4, 25.1, 24.5 and 23.1%, respectively. Unfortunately, 26% of patients did not use antihypertensive medication, and 34.2% of patients failed to achieve the target blood pressure. This means that caution should be paid to cancer patients before the application of VEGF signalling inhibitors. There was a 20-fold increase in CVD-related deaths among patients with cancer between 2000 and 2016 in Korea, and the risk of CVD should be monitored in cancer survivors [2]. Although VEGF signalling inhibitors can be prescribed to advanced cancers in general, risk assessment of CVD in long survivors might also be important for keeping quality of life. I present information regarding the risk of CVD in patients with differentiated thyroid cancer as an example.

Zoltek *et al.* [3] reported that the standardized incidence ratio [95% confidence interval (95% CI)] of atrial fibrillation in patients with differentiated thyroid cancer was 1.66 (1.41–1.94). Although differentiated thyroid cancer presents a good prognosis, adequate screening of CVD is needed for long survivors. Klein Hesselink *et al.* [4] reported that the age and sex-adjusted hazard ratios (95% CIs) of 1-SD increase in log-transformed N-terminal pro brain natriuretic peptide in patients with differentiated thyroid cancer for CVD events and all-cause mortality were 3.22 (2.17–4.79) and 1.61 (1.17–2.23), respectively. Appropriate biomarkers might be effective for monitoring and preventing CVD.

Regarding the mechanism of CVD in patients with differentiated TC, Klein Hesselink *et al.* [4] speculated that a chronic suppression of thyroid-stimulating hormone might induce cardiac damage and increase the risk of CVD. Pajamäki *et al.* [5] also reported that the risk of atrial fibrillation increased significantly in patients with a mean thyroid-stimulating hormone level of less than 0.1 mU/l and with radioiodine treatment. There is a possibility that thyroid dysfunction may contribute to the relationship between differentiated thyroid cancer and subsequent CVD events. However, further prospective studies are needed in patients with differentiated thyroid cancer to verify the risk of CVD with focus on thyroid cancer treatment.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Liu F, Hidru TH, Gao R, Lin Y, Liu Y, Fang F, *et al.* Cancer patients with potential eligibility for vascular endothelial growth factor antagonists use have an increased risk for cardiovascular diseases comorbidities. *J Hypertens* 2020; 38:426–433.
2. Oh CM, Lee D, Kong HJ, Lee S, Won YJ, Jung KW, *et al.* Causes of death among cancer patients in the era of cancer survivorship in Korea: attention to the suicide and cardiovascular mortality. *Cancer Med* 2020; 9:1741–1752.
3. Zoltek M, Andersson TM, Hedman C, Ihre-Lundgren C, Nordenvall C. Cardiovascular incidence in 6900 patients with differentiated thyroid cancer: a Swedish nationwide study. *World J Surg* 2020; 44:436–441.
4. Klein Hesselink EN, van der Horst-Schrivers ANA, van der Horst ICC, Bakker SJL, Muller Kobold AC, Brouwers AH, *et al.* NT-proBNP is increased in differentiated thyroid carcinoma patients and may predict cardiovascular risk. *Clin Biochem* 2017; 50:696–702.
5. Pajamäki N, Metso S, Hakala T, Ebeling T, Huhtala H, Ryödi E, *et al.* Long-term cardiovascular morbidity and mortality in patients treated for differentiated thyroid cancer. *Clin Endocrinol (Oxf)* 2018; 88:303–310.

Journal of Hypertension 2021, 39:2122–2123

Department of Hygiene and Public Health, Nippon Medical School, Tokyo, Japan

Correspondence to Tomoyuki Kawada, MD, PhD, Department of Hygiene and Public Health, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-Ku, Tokyo 113-8602, Japan. Tel: +81 3 3822 2131; fax: +81 3 5685 3065; e-mail: kawada@nms.ac.jp

DOI:10.1097/HJH.0000000000002975

OPEN

Reply

Fei Liu, Tesfaldet H. Hidru, Xiaolei Yang, and Yunlong Xia

We read the correspondence letter by Kawada about the increased risk for cardiovascular diseases comorbidities in cancer patients with potential eligibility for vascular endothelial growth factor (VEGF) antagonist use with great interest [1]. Kawada highlighted the high risk of cardiovascular diseases (CVDs) and CVD-related mortality among cancer patients with a focus on thyroid cancer. Their article elucidated the mechanism between CVD and thyroid cancer and justified the need to verify the risk of CVD in patients with differentiated thyroid cancer to improve on the disease management. According to his hypothesis, thyroid dysfunction may contribute to the relationship between differentiated thyroid cancer and subsequent CVD events.

Currently, high rates of CVD in cancer patients are a well established phenomenon; thus, the risk of CVD should be monitored in cancer survivors. The risk of CVD post antitumor drugs, for example VEGF has been reported previously [2]. Although VEGF signalling inhibitors is indicated for advanced

stage cancers with a relatively short life expectancy, a risk assessment of CVD may be important to maintain a good quality of life. For example, appropriate biomarkers might be effective for the monitoring and prevention of CVD. However, many issues related to clinically applicable biomarkers remain unresolved. For instance, Kawada mentioned N-terminal pro-brain natriuretic peptide (NTproBNP), which is the golden standard for the diagnosis of congestive heart failure, was found to be positively associated with CVD events and all-cause mortality in patients with differentiated TC as well [3,4]. Therefore, further study is needed to verify whether NTproBNP levels can serve as screening markers at different stages of CVD in cancer patients.

In our study, cancer patient, with a potential indication for the treatment of VEGF signalling pathway inhibitors, generally carry a high burden of CVD-related comorbidity [5]. Existing hypertension was the most prevalent comorbid condition, accounting for 23.1% in thyroid cancer patients. In study by Kawada, 26% of patients did not use antihypertensive medication, and 34.2% of patients failed to achieve the target blood pressure. Although these statistics highlighted the need for strict hypertension management in cancer patients, it should be interpreted with caution. For instance, the prevalence of CVD in hypertension patients with acute and advanced cancer will vary throughout follow-up due to changes in disease condition, cardiovascular risk factors and cardiovascular effects of the treatment prescribed. Overall, our study team agrees with Kawada about the growing risk of CVD among cancer patients. Therefore, early prediction of CVD among cancer patients is vital to improve their prognosis.

It is becoming increasingly recognized that cancer is the primary driver behind the health outcomes linked to CVD. Emerging evidence suggests an intimate relationship between CVDs and cancer, which may result from several shared risk factors such as inflammation, reactive oxygen species and so on [6]. Interestingly, Kawada hypothesized a possible connection for increased risk of CVD in thyroid cancer patients. Regarding the mechanism of CVD in patients with differentiated thyroid cancer, the chronic suppression of thyroid-stimulating hormone might induce cardiac damage and increase the risk of CVD [3]. However, whether there is a causal relationship between thyroid dysfunction and CVD remains uncertain. Therefore, more emphasis should be placed on the screening of thyroid dysfunction among hypertensive patients with thyroid cancer before the use of VEGF antagonists. Follow-up studies are needed to investigate the possible pathways that explain the mechanism underlying thyroid dysfunction in hypertension with thyroid cancer.

ACKNOWLEDGEMENTS

The authors have indicated no financial support.

Conflicts of interest

There is no conflicts of interest in this study.

REFERENCES

1. Kawada T. Cancer, hypertension and risk for cardiovascular disease. *J Hypertens* 2021; 39:2122.
2. Schmidinger M. Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors. *EJC Suppl* 2013; 11:172–191.
3. Klein Hesselink EN, van der Horst-Schrivers ANA, van der Horst ICC, Bakker SJL, Muller Kobold AC, Brouwers AH, *et al*. NT-proBNP is increased in differentiated thyroid carcinoma patients and may predict cardiovascular risk. *Clin Biochem* 2017; 50:696–702.
4. Paget V, Legedz L, Gaudebout N, Girerd N, Bricca G, Milon H, *et al*. N-terminal pro-brain natriuretic peptide: a powerful predictor of mortality in hypertension. *Hypertension* 2011; 57:702–709.
5. Liu F, Hidru TH, Gao R, Lin Y, Liu Y, Fang F, *et al*. Cancer patients with potential eligibility for vascular endothelial growth factor antagonists use have an increased risk for cardiovascular diseases comorbidities. *J Hypertens* 2020; 38:426–433.
6. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation* 2016; 133:1104–1114.

Journal of Hypertension 2021, 39:2122–2123

First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning Province, China

Correspondence to Yunlong Xia, PhD, Department of Cardiology, Institute of Cardiovascular Diseases, First Affiliated Hospital of Dalian Medical University, Dalian 116011, China. Tel: +86 18098875555; e-mail: yunlong_xia@126.com

DOI:10.1097/HJH.0000000000002971