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COMMENTARY

Does chronic hypertension prevent cancer progression?

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Gliomas are the most common type of primary brain tumor, among which glioblastoma multiforme (GBM) is the most aggressive and fatal subtype. GBMs are highly vascularized and are one of the most vascularized of all solid tumors.[1] Although the standard therapy for a newly diagnosed GBM involves maximal surgical resection, radiotherapy and chemotherapy, anti-angiogenic therapies (including anti-vascular endothelial growth factor (VEGF) monoclonal antibody and a number of orally administered small-molecular agents) are also used against GBM, especially for the treatment of recurrent GBM.[2] However, hypertension is a common adverse event in patients taking anti-angiogenic drugs. Hypertension is reported to be an effective biomarker of therapeutic efficacy in patients with GBM.[3] The mechanism of anti-angiogenic therapy-induced hypertension is thought to be the inhibition of nitric oxide production via inhibition of PI3K-Akt-eNOS activity in endothelial cells. However, how the development of hypertension in GBM patients undergoing anti-angiogenic therapy affects the mortality of these patients compared with hypertensive GBM patients without this therapy is poorly understood.

Chronic hypertension (CH) is an important risk factor that leads to small vessel disease in the brain and results in impaired microcirculation. Spontaneously hypertensive rats (SHRs) are a commonly used model that reflects human cerebral small vessel disease,[4] and they present with impaired angiogenesis.[5] Hirashima *et al.*[6] reported that high blood pressure may be additively implicated with bilateral notching of the uterine arteries in circulating abnormalities of angiogenesis-related factors. Moreover, treatment with cilostazol is reported to prevent neuronal dysfunction in the stroke-prone SHR model (SHRSP), with an increase in angiogenesis via increased VEGF levels,[7] indicating that angiogenesis is relatively attenuated in a chronic hypertensive state. Because the primary therapeutic goal in cardiovascular disease is to increase angiogenesis (contrary to the therapeutic goal in cancer), there are several reports assessing the relationship between CH and cancer progression using animal models. In clinical practice, the relationship between hypertension and cancer has been primarily discussed with regard to drug-induced hypertension but not the mortality of cancer patients with hypertension.

The present study by Letourneur *et al.*[8] investigated whether CH may reduce GBM progression using the SHR model. They implanted rat glioma C6 tumor cells in the caudate–putamen of either SHRs or Wistar-Kyoto rats (the latter as normotensive controls) and evaluated tumor growth by magnetic resonance imaging. Interestingly, they observed that SHRs showed significant attenuation of tumor growth, whereas the cerebral blood volume and cerebral blood flow were greater in the SHRs with tumors. They speculated that the reason for this difference was partly due to the impaired angiogenesis as a result of CH. Sustained blood pressure elevation and pressure fluctuations in small cerebral vessels result in microvascular damage;[9] however, microvascular dysfunction may attenuate tumor growth because of the decreased microcirculation. From their findings, it is suggested that tumor progression, especially in the brain, is slow, and mortality due to brain tumors is also low in chronic hypertensive patients. To our knowledge, there are few reports to date that assess either tumor progression or brain metastasis in hypertensive patients.

Hypertension is not only the major risk factor for stroke and small vessel disease (which leads to vascular dementia), but is also an inducing factor of cerebral hemorrhage, ischemic stroke and other complications. Therefore, this finding does not contribute to identifying a new treatment option for GBM, but rather, suggests the possibility of reduced tumor progression in chronic hypertensive patients. CH-induced impairment of microcirculation may occur in other local tissues aside from the brain, and thus, the present study results suggest that cancer progression and metastasis may be slower in the elderly than in young people.

The effect of antihypertensive drugs on the incidence and progression of cancer has been discussed. Because the protective effect of antihypertensive drugs on the vasculature prevents endothelial dysfunction and maintains the microcirculation, this beneficial effect may affect patients in whom cancer already exists, but the details regarding the mechanism are an enigma. The authors used the SHR but not SHRSP model in the present study. Jesmin *et al.*[10] reported that the expression level of VEGF differs between the SHR and SHRSP models during cardiac remodeling. Therefore, further analysis is necessary to observe the results of similar studies in SHRSP rats. Furthermore, we would like to know whether similar attenuation of cancer progression occurs in other implanted carcinoma cell lines. The present study, which focused on the relationship between CH and cancer progression, is expected to enhance cancer treatment in the elderly.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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