Hypertension in Patients with Cancer

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Abstract

There is a known association between chemotherapy and radiotherapy for treatment of cancer patients and development or worsening of hypertension. The aim of this article is to review this association. A literature search was conducted for articles reporting this association on the databases PubMed, SciELO and LILACS between 1993 and 2013. There was a high coprevalence of hypertension and cancer, since both diseases share the same risk factors, such as sedentary lifestyle, obesity, smoking, unhealthy diet and alcohol abuse. The use of chemotherapy and adjuvant drugs effective in the treatment of cancer increased the survival rate of these patients and, consequently, increased the incidence of hypertension. We described the association between the use of angiogenesis inhibitors (bevacizumab, sorafenib and sunitinib), corticosteroids, erythropoietin and non-steroidal anti-inflammatory drugs with the development of hypertension. We also described the relationship between hypertension and carotid baroreceptor injury secondary to cervical radiotherapy. Morbidity and mortality increased in patients with cancer and hypertension without proper antihypertensive treatment. We concluded that there is need for early diagnosis, effective monitoring and treatment strategies for hypertension in cancer patients in order to reduce cardiovascular morbidity and mortality.

Introduction

The main factor determining the epidemiological growth of cardiovascular diseases (CVD) and neoplastic diseases in Brazil is demographic, determined by a greater proportion of the population reaching senility. Cancer and CVD share a high coprevalence, due the occurrence of risk factors common to both conditions[1]. Common risk factors for cancer and CVD include smoking, unhealthy diet and obesity, physical inactivity, diabetes mellitus, hypertension and alcohol abuse[1]. These risk factors alone or in combination are the main triggers for the development of cancer and are the same factors that expose individuals to the risk of developing the most prevalent CVD[1,2]. In contrast, the coincidence of risk factors allows implementation of integrated prevention strategies for most non-transmissible chronic diseases[2]. Before the introduction of angiogenesis inhibitors (AI) in chemotherapeutic treatment, the prevalence of hypertension in patients with cancer was similar to that in the general adult population[3,4]. However, increased access to the modern chemotherapeutic arsenal and the consequent prolonged survival of patients with cancer has had an impact on the development or worsening of hypertension, particularly in patients treated with AI[3-5]. The presence of hypertension prior to cancer treatment, as well as any other CVD such as as ischemic disease, valvular disease, or arrhythmias, predicts the development of myocardiopathy due to use of chemotherapeutic drugs[3,6,7]. Hypertension is the most frequently recorded comorbidity in patients with cancer, and its incidence increases with chemotherapeutic treatment, particularly with AI – bevacizumab, sunitinib, sorafenib, vatalanib, pazopanib, motesanib, axitinib and aflibercept[6]. Other medications used in cancer patients such as erythropoietin, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), as well as injury to the carotid baroreceptor by cervical radiotherapy, can also increase blood pressure[3].

This subject has not been much discussed among cardiologists and clinicians. Evidences from the literature still derive from analysis of secondary outcomes or retrospective studies. The aim of this study was to review the association between chemotherapeutic treatment, adjuvant drugs in cancer treatment and radiotherapy with the development or worsening of hypertension. It also aimed at emphasizing the specificities of the diagnostic criteria, monitoring and treatment of the hypertensive patient with cancer.

Methods

A systematic literature review was performed on the databases PubMed, SciELO and LILACS. Keywords such as “angiogenesis inhibitors”, “bevacizumab”, “sorafenib”, “sunitinib”, “erythropoietin”, “corticosteroids”, “non-steroidal anti-inflammatory drug”, “baroreceptor” and “radiotherapy” were correlated with “hypertension” and “cancer”. Inclusion criteria were articles published from 1993 to 2013 in English, Spanish and Portuguese. Observational clinical studies, such as cohort, case-control and cross-sectional studies, were included. Reviews and editorials were included when deemed relevant and related to the topic. Publications from the MD Anderson Cancer Center and Texas Heart Institute of University of Texas, TX, USA - reference institutions in the study of cardio-oncology - were included, even if as part of a textbook. The recommendations of the I Brazilian Guideline of Cardio-Oncology of the Brazilian Society of Cardiology[3] were observed.

Keywords

Hypertension; Neoplasms / complications; Neoplasms / drug therapy; Neoplasms / radiotherapy; Antihypertensive Agents; Indicators of Morbidity and Mortality.

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Chemotherapy and Hypertension

Angiogenesis inhibitors

Angiogenesis inhibitors are divided into two main groups: monoclonal antibodies that target vascular signaling pathways (bevacizumab) and small molecule inhibitors of tyrosine kinase (sunitinib, sorafenib). The mechanism by which these drugs induce hypertension is not completely understood, but can be directly related to the inhibition of vascular endothelial growth factors (VEGF) signaling via tyrosine kinase[6,7]. VEGF signaling is important for proper endothelial functioning and nitric oxide synthesis – its inhibition impairs vasodilation[1,6-8]. Other effects of VEGF inhibition include induction of endothelial cell death and rarefaction of resistance vessels[7,8]. The aim of AI therapy is to target molecules with increased expression in patients with cancer. However, such molecules are also present in non-tumoral cells and have a physiological role in several systems, including the cardiovascular system[8]. Therefore, when acting in the tumor by inhibiting VEGF, AI also causes hypertension. This generates a paradox, since the presence of hypertension is simultaneously an adverse cardiovascular effect and a sign of favorable oncological therapeutic response[8]. Table 1, adapted from Yeh et al.[6], presents the incidence and frequency of use of the main AI associated with the development of hypertension.

Bevacizumab

Bevacizumab is an AI that belongs to the group of monoclonal antibodies that target vascular signaling pathways[5,9]. Its main function is VEGF inhibition[10]. The pathogenesis of the hypertensive effect associated with bevacizumab is not yet completely understood, but is believed to be caused by interference with blood pressure homeostatic factors, leading to endothelial dysfunction, capillary rarefaction and inhibition of the nitric oxide pathway, increasing vasoconstriction and decreasing renal excretion of sodium[5]. Its main use is in the treatment of solid neoplasias, such as gastrointestinal tumors, metastatic renal carcinoma[8,10] and glioblastoma[9]. It is also used as first-line treatment in metastatic colorectal cancer[8] and advanced non-oat cell lung cancer[3,8].

Ranpura et al.[11] analyzed 12,656 patients with 20 types of solid tumors included in a meta-analysis and concluded that the incidence of hypertension in patients treated with bevacizumab was 23.6% (95% confidence interval [CI]: 20.5–27.1%), of which 7.9% (95% CI: 6.1–10.2%) developed grade 3 or 4 hypertension. The incidence of grade 3 or 4 hypertension varies according to the malignancy and the type of cancer, dose of bevacizumab, interaction with other antineoplastic drugs and response to antineoplastic treatment[5,8,9,11]. Risk factors for development of hypertension are age above 75 years, Afro-descendant ethnicity and, particularly, kidney tumors[8]. The toxic dose of bevacizumab for development of hypertension has been reported in patients using 2.5 mg/kg/week with a risk ratio (RR) of 4.78 (95% CI: 3.59-6.36), as well as 5 mg/kg/week with a RR of 5.39 (95% CI: 3.68-7.90). Lower doses of bevacizumab (0.5 mg/kg/min) are not associated with risk of developing hypertension and proteinuria[12]. It is important to highlight that the development of hypertension associated with bevacizumab is a biomarker of effective inhibition of VEGF signaling[5,9]. Patients who develop grade 2 and 3 hypertension present antitumoral activity and event-free survival of 14.1 months compared with 3.1 months in those who do not develop hypertension[5]. Discontinuation of treatment for hypertension and need of hospitalization occur in 1.7% of the patients. Complications such as hypertensive encephalopathy and central nervous bleeding are associated with a RR of 3.16 (95% CI: 0.91-10.9)[5,11]. Use of anthracyclines and/or radiotherapy associated with treatment with bevacizumab increase the risk of arterial thromboembolic events[8]. Bevacizumab is also used in some neovascular proliferative ophthalmic diseases, such as age-related macular degeneration (AMD). The physiopathology of this ophthalmic disease involves neovascular growth via VEGF. Therefore its inhibition by intravitreal bevacizumab injection slows down vascular growth with good clinical and ophthalmic results without systemic action such as increase in blood pressure in clinical follow-up of 6 weeks[11,13]. Treatment with anticoagulants, ACE inhibitors and dihydropyridine calcium channel blockers may help protect from the vascular effects promoted by bevacizumab[8].

Sorafenib

Sorafenib is an AI that belongs to the group of small molecule tyrosine kinase inhibitors[14,15]. Hypertension is the basic mechanism of toxicity of this drug, which acts on the inhibition of VEGF. Cutaneous adverse reactions, such as rash and desquamation, and gastrointestinal reactions, such as diarrhea, are also described. Sorafenib is recommended and approved for treatment of advanced renal cell carcinoma[14], hepatocellular carcinoma[8,15], metastatic melanoma[7], non-oat cell carcinoma of the lung[8] and advanced thyroid carcinoma refractory to radioactive iodine treatment.

The incidence of hypertension ranges from 14% to 43% during treatment with sorafenib in some clinical trials. Of these, grade 3 or 4 hypertension has been seen

Table 1 – Incidence and frequency of use of the main angiogenesis inhibitors associated with the development of hypertension

Chemotherapeutic agents	Incidence (%)	Frequency of use
Bevacizumab	35	+ +
Sorafenib	17-43	+ + +
Sunitinib	5-47	+ + +

Adapted from Yeh and cols.[6]

in 1.4% to 38.0%[6,16,17]. A recent meta-analysis including 45,599 patients treated with sorafenib concluded that the overall incidence of hypertension was 23.4%, 2.1% to 30.7% of which were grade 3 or 4[18]. The incidence rates of hypertension are comparable to other AI such as sunitinib and bevacizumab for treatment of renal carcinoma and other types of tumors[14]. The hypertensive effect is mediated by vascular rarefaction and change in nitric oxide production associated with endothelial dysfunction[8]. Experiments suggest that the damage to the mitochondrial energetic metabolism is the key factor to the cardiotoxic effect mediated by sorafenib[9]. Increase in blood pressure develops in the first three weeks of therapy with sorafenib and persists for up to 18 weeks. The dose of sorafenib should be corrected or suspended according to adverse response to treatment such as: treatment-refractory hypertension, bleeding, severe skin reactions, refractory diarrhea and myocardial ischemia or infarction.

Sunitinib

Sunitinib is also an AI and, like sorafenib, belongs to the group of small molecule tyrosine kinase inhibitors[19]. It is used for treatment of renal cell carcinoma[8,20], gastrointestinal stromal tumors (GIST)[8,21] and neuroendocrine pancreatic tumors. The inhibition of the development of new blood vessels, mediated by VEGF inhibition, is the main strategy to treat solid tumors[22].

Use of this drug is closely associated with the development of hypertension. In some clinical trials, its incidence ranges between 5% and 24%[23,24]. A retrospective analysis showed increased blood pressure in the first four weeks, with levels of 150X100 mmHg in 47%, whereas only 17% had grade 3 hypertension[8,25]. Some evidences point to the ratio of the increase in blood pressure as a biomarker of response to chemotherapy[21,22,26]. A study[20] evaluated patients with metastatic renal cell carcinoma in which 54.8% had a hypertensive response to chemotherapy with sunitinib. The average event-free survival in the hypertensive group was 15.5 months (95% CI: 10.9–13.7 months) compared with 2.5 months (95% CI: 2.3–3.8 months) in the group without hypertension, whereas the average overall survival was 30.9 months (95% CI: 27.9–33.7 months) *versus* 7.2 months (95% CI: 5.6–10.7 months), respectively[20]. A similar study[21] with GIST patients treated with sunitinib showed results consistent with the hypothesis of hypertension as a biomarker of chemotherapeutic response.

Hypertension and heart failure with treatment with tyrosine kinase inhibitors

Patients who developed ventricular dysfunction or heart failure after treatment with sunitinib for metastatic renal carcinoma had previous hypertension caused or exacerbated by this chemotherapeutic agent. Heart failure occurs in individuals with hypertension grade 3 or higher. There are still only a few studies that reveal the physiopathological mechanism of cardiotoxicity in these patients. However, clinical evidences indicate that hypertension precedes or contributes to cardiac myocytes injury which culminates in ventricular dysfunction[8]. Therefore, it is reasonable to infer that the treatment of hypertension in these patients prevents the development of ventricular dysfunction.

Drugs adjuvant in cancer treatment

Erythropoietin

Erythropoietin (EPO) is a glycoproteic hormone that controls bone marrow erythropoiesis. It is produced by renal fibroblasts and hepatic perisinusoidal stellate cells. In adulthood, it is produced mostly by the kidney, since hepatic production is limited to fetal and neonatal stages. Recombinant human EPO (rhuEPO) is often used in chronic renal patients with acquired immune deficiency syndrome and/or cancer. Anemia is a frequent complication in cancer patients[27]. Up to 70% of these patients present anemia at some stage of their disease or treatment. Anemia can be one of the early signs of neoplastic disease, but is more commonly associated with antineoplastic treatment or disease progression. The incidence and severity of anemia depend on the type of tumor, patient's age, disease stage, and type and intensity of antineoplastic treatment[27]. A consensus elaborated by the American Society of Clinical Oncology and American Society of Hematology recommends the use of rhuEPO in patients with hemoglobin < 10 g/dL, whereas for those with hemoglobin between 10 and 12 g/dL, the decision should be determined by clinical circumstances[28]. For patients with anemia associated with cancer and chemotherapy, the recommended starting dose is 150 IU/kg administered subcutaneously three times a week for eight weeks. If the response is not satisfactory after eight weeks, the dose may be doubled[28].

About 33% to 35% of the patients treated with rhuEPO show increased peripheral vascular resistance and a mild decrease in cardiac output, with consequent elevation in blood pressure levels[29,30]. Hypertension occurs 2 to 16 weeks after use of rhuEPO. Several physiopathological mechanisms have been proposed to explain the development of hypertension. Among them, we can highlight: (1) increase in erythrocyte mass with increase in blood viscosity; (2) change in production and sensitivity of endogenous vasopressor agents; (3) change in the vascular smooth-muscle ionic milieu hindering response to vasodilating factors; (4) direct vasopressor effect of rhuEPO; and (5) remodeling through stimulation of vascular cell growth[31]. Usual antihypertensive medications are used in the treatment of hypertension associated with rhuEPO. In patients with chronic kidney disease, calcium antagonists and alpha-adrenergic receptor blockers present good results. However, angiotensin-converting enzyme (*ACE)* inhibitors and angiotensin II receptor blockers (*ARBs*) have shown little efficacy due to the suppression of angiotensin II activity. Diuretics have little activity in patients with advanced kidney disease. If pharmacological measures are ineffective in controlling hypertension, the dose of rhuEPO may be reduced to half or even temporarily suspended[32].

NSAIDs and hypertension in cancer treatment

Two large meta-analyses covering more than 90 clinical trials have shown that NSAIDs may increase blood pressure[33].

The main physiopathological effect is considered to be the inhibition of prostaglandins (PG) and the decrease in renin. It has been proposed that the inhibition of natriuretic PG and the consequent retention of sodium could explain the pressor effect. Another explanation would be the inhibition of the direct vasodilatory effect of PG on renal and extrarenal vascular beds. However, the increase in sodium and water retention concomitant with an increase in vascular resistance caused by exacerbation of endothelin-1 synthesis by the kidney is potentially important. Both in experimental animals and in humans, colorectal, gastric and esophageal tumors express high levels of cyclooxygenase-2 (COX-2), unlike the normal intestinal mucosa. Such findings raise the possibility of involvement of COX-2 in the progression and dissemination of cancer, since stimulation of PGE-2 by COX-2 inhibits tumor suppressive activity and stimulates proliferation of epithelial cells. COX-2 has a close relationship with the regulation of tumor angiogenesis; such fact is already well established in the progression and dissemination of prostate cancer. Several studies have shown that NSAIDs can reduce the progression of and/or act prophylactically in some intestinal tumors, through mechanisms dependent or not on their ability to inhibit COX-2[34].

The elevation in blood pressure during treatment with NSAIDs occurs is greater in elderly patients, Afro-descendants and in those with low renin levels[35]. In an analysis by Pope et al.[33], indomethacin and naproxen increased the average blood pressure by 3.59 mmHg and 3.74 mmHg, respectively. Piroxicam was associated with a non-significant increase of 0.49 mmHg in the average blood pressure. A meta-analysis by Johnson et al.[33] showed that NSAIDs increase the average supine blood pressure by 5.0 mmHg. Piroxicam was associated with the highest increase (6.2 mmHg). Acetylsalicylic acid, sulindac and flurbiprofen showed lower elevations in blood pressure. Indomethacin and ibuprofen exerted intermediate effects. The antihypertensive action mediated by the synthesis of vasodilating PG induced by diuretics, ACE inhibitors and adrenergic beta-blockers decreased when these drugs were associated with NSAIDs. The antihypertensive effects of calcium channel blockers and angiotensin II receptors antagonists suffered less interference of NSAIDs[36,37].

Corticoids and hypertension in cancer treatment

Glucocorticoids (GC) are substances derived from cholesterol, synthesized and secreted by the adrenal glands. These hormones act on the transcriptional control of genes involved in regulation of metabolic, cardiovascular and immunological functions[38]. Corticosteroids seem to act as physiological regulators of COX-2 mRNA expression, which might explain in part the immunosuppressive characteristic of this enzyme[34]. In early 1950, the discovery of the potent anti-inflammatory effect of GC led to use of these agents on the treatment of chronic rheumatic diseases. Currently, synthetic GC are often used in the treatment of autoimmune diseases, in the prevention of allograft rejection and as adjuvants in some chemotherapeutic treatments, since their effect prolong immunosuppression. As an example, the most frequently used regimens in the treatment of non-Hodgkin's lymphoma are CVP (cyclophosphamide, vincristine, and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). However, chronic use of GC is associated with various adverse cardiometabolic effects[39,40]. In Cushing's syndrome, there is retention of sodium and water due to high blood levels of cortisol. This is the main factor responsible for the development of secondary hypertension in 80% of the cases. Chronic use of GC also induces insulin resistance, diabetes mellitus and dyslipidemia[41]. If untreated, Cushing's syndrome can progress to death due to cardiovascular disease[39,41]. The treatment of the adverse effects of GC use is the reduction in corticotherapy associated with control of fluids and salt, diet and use of diuretics. Other classes of antihypertensive drugs can be added, such as angiotensin II inhibitors, calcium channel antagonists and central sympatholytics[40]. Use of GC in low doses for long periods of time does not seem to trigger hypertension.

Carotid baroreceptor injury by cervical radiation therapy

Chemotherapy treatment associated with radiotherapy has increased survival of patients with head and neck cancer and are now associated with late complications. The arterial baroreceptors have a tonic inhibitory effect on the sympathetic tone, thus controlling the total peripheral resistance and the cardiac output[42]. Other evidences, however, show that the modulation of the heart rate by baroreceptors is due primarily to the cardiovagal activation triggered by stimulation of vagal neurons located in the nucleus ambiguus and in the vagal dorsal motor nucleus[43]. As a result, dysfunction in the baroreceptors is associated with increased sympathetic activity and, mainly, reduction of parasympathetic activity, resulting in increased heart rate and increasing the variability of the blood pressure[44]. In summary, studies in humans show that the lability of the blood pressure, unsustained hypertension, orthostatic intolerance and tachycardia by failure in the baroreceptor mechanism may occur in bilateral or unilateral carotid baroreceptor denervation following endarterectomy, cervical trauma, tumor resection and radiotherapy[44]. Differential diagnosis with pheochromocytoma should be considered[44]. Another mechanism of baroreflex dysfunction due to late effects of radiation is considered to be an acceleration of the process of atherosclerosis and chronic hypertension[44,45,46]. Therefore, it is known that baroreflex dysfunction caused by diabetes mellitus correlates clearly with the occurrence of sudden death in these patients[46]. In a similar reasoning, but without corroborative evidence, other causes of dysfunction in cardiovascular control, such as the lesion caused by radiotherapy, are considered as also increasing the risk of sudden death.

Diagnosis of hypertension in the cancer patient

Diagnostic criteria of hypertension in patients with cancer are defined according to the National Cancer Institute of the United States of America and relies on a system of classification of adverse events, the Common Toxicity Criteria (NCI CTC)[3], which is based on the severity of the event and

in the intervention required for its control. The level of blood pressure considered suitable in the cancer patient is similar to that recommended for the adult population[3].

During chemotherapy treatment, blood pressure assessments are recommended before, during, at the end of the drug infusion and 1 hour later[3]. Regarding the use of AI, the National Cancer Institute recommends weekly blood pressure monitoring during the first cycle of chemotherapy and then at least every two to three weeks during treatment[3,7]. After this phase, if the blood pressure remains stable and there are no adverse cardiovascular complications, monitoring may be aligned with routine clinical assessments or during home blood pressure monitoring[3]. Due to nephrotoxic effects, mainly associated with sunitinib, it is important to test for abnormal urinary elements and urinary sediment for early detection of proteinuria[3,4].

Treatment of hypertension in cancer patients

Treatment goals for hypertensive patients with cancer do not differ from those in other hypertensive patients, *i.e.*, focus on three targets: 1) identify the causes of the hypertension; 2) assess lifestyle and recognize cardiovascular risk factors or comorbidities that may affect the prognosis or guide the choice of treatment; and 3) assess the presence or absence of target organ injury associated with hypertension[7]. Hygienic and dietary measures should always be encouraged, with guidance on the practice of physical activity, low-sodium diet and body weight control. However, in some oncological patients with advanced disease stages, these strategies are not sufficient or fully enforceable. Pharmacological treatment of hypertension is reserved for cancer patients with hypertension, or for those who develop hypertension during chemotherapy, guided by the recommendations of the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 8)[47] and the I Brazilian Guideline of Cardio-Oncology[3]. Early pharmacological intervention should be advocated in these groups[3,8]. Blood pressure targets according to the VI Brazilian Hypertension Guidelines are classified according to the risk category and therapeutic target to be achieved. With blood pressure control and monitoring during chemotherapy, and prevention of cardiovascular adverse events, patients can tolerate chemotherapy treatment up to the maximum recommended dose, benefiting from more effective tumor control which allows improvement in life quality and longevity[3].

The primary goal of blood pressure treatment is to reduce morbidity and mortality and cardiovascular risk associated with injury of target organs[7]. Discontinuation of AI due to development of hypertension, particularly in grade 3 patients, is controversial since hypertension is associated with better response to antineoplastic treatment[7]. Therefore, maintenance of chemotherapy and effective blood pressure control with antihypertensive drugs are recommended.

In the choice of antihypertensive agent, there is evidence that some are more effective than others, given that the biological effects of these medications differ from those of angiogenesis[7]. Therefore, ACE inhibitors may be beneficial as first-line treatment, since they reduce proteinuria and expression of plasminogen activator inhibitor-1[7]. *In vivo* studies have demonstrated the potential of ACE inhibitors in reducing microcirculatory changes, decreasing catabolism of bradykinins and increasing release of endothelial nitric oxide[6]. Nondihydropyridine calcium channel blockers - verapamil and diltiazem - inhibit the cytochrome P450 system and should not be administered concomitantly with AI, since they are metabolized by cytochrome P450 3A4[3,6,7]. Phosphodiesterase inhibitors or nitrates may increase nitric oxide levels and, theoretically, would have antihypertensive activity on sorafenib-associated hypertension. However, such drugs have not been validated for clinical treatment of hypertension[6,7].

Considering that hypertension is a risk factor for development of heart failure and is often its etiology or comorbidity, medications that reduce the morbidity and mortality in patients with heart failure - carvedilol, metoprolol, bisoprolol, ACE inhibitors and ARBs - should be considered first-line agents in the treatment of AI-associated hypertension[3,7].

Conclusion

The increasing prevalence of cancer imposes considerations regarding development and implementation of cardiovascular diagnostic and treatment strategies in clinical practice. Cancer patients undergoing chemotherapy require cardiovascular monitoring, including systematic measurement of blood pressure. With early diagnosis and adequate treatment of hypertension, cancer patients can tolerate maximum doses of the planned chemotherapeutic drugs, without injury to target organs, yielding better control of the tumor.

Author contributions

Conception and design of the research:Martins WA. Acquisition of data: Souza VB, Martins WA. Writing of the manuscript: Souza VB, Martins WA. Critical revision of the manuscript for intellectual content: Souza VB, Silva EN, Ribeiro ML, Martins WA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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