Management of Intracranial Stenotic Disease in Cancer Patients Treated With Vasotoxic Agents

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Objective: To summarize the characteristics of and therapeutic options for cancer patients whose treatments may be vasotoxic and cause intracranial arterial stenotic disease and stroke. *Methods:* We describe 3 patients with symptomatic cerebrovascular pathology that were being actively treated for cancer. *Results:* Two of the patients were being treated with tyrosine kinase inhibitors (TKIs); and the third was being treated with 2 monoclonal antibodies, one of which was targeting an endothelial growth factor. These agents have been associated with vascular adverse events. Surgical revascularization was done in the first 2 patients, as they were suffering from cerebral ischemia. The third patient had suffered a significant brain hemorrhage, and therapeutic options were limited. In the first 2 patients, treatments also included antiplatelet agents and stopping/changing the TKI. In one of these patients we demonstrated regression of arterial stenosis after changing the TKI. *Conclusions:* Possibilities for treatment in this population, beyond the usual medical and surgical administrations, may include stopping or changing cancer drugs that may be related to the development of arterial pathology. Collaboration with oncologists is essential in this subset of patients. While aware of the potential for vascular toxicity, oncologists are often not fully appreciative of the fact that their therapeutic agents can cause stroke.

Key Words: Stroke—cancer—immunotherapy—targeted therapy—moyamoya

Introduction

Cancer remains dangerous and potentially fatal for many patients. Cure rates have been improving; so has survival, perhaps a more important metric. For many, cancer has become a chronic disease. Not curable but not imminently fatal, it is something that these patients now have to live with. Newer therapies, which target cellular growth on a molecular level, have resulted in large numbers of patients surviving long-term, but often dependent on the continued administration of drugs to control the cancer.

Not only do today's physicians and surgeons have to be aware of how cancer can affect the body, but also of how the drugs responsible for many of these long-term remissions can play havoc. The therapeutic agents are tremendously variable, ranging and size and characteristic from small molecules with molecular weights of less than 500 Da to monoclonal antibodies (mAB) in the range of 150 kDa. Some are more specific, or cleaner, than others; but all have the potential to cause adverse events. Recently, attention has been focused on the management of their untoward effects.

Vascular toxicity, including stroke, is being recognized as a potential problem with several agents, especially those that affect angiogenesis, platelet function, and/or the coagulation cascade. Alterations in these physiological functions can lead to endothelial dysfunction and thromboembolic problems. While oncologists understand the mechanism of action and potential troubles associated with these drugs, other providers are not necessarily as up-to-date. The purpose of this paper is to describe the management of a small cohort of cancer patients who presented with stroke and intracranial steno-occlusive vascular disease suggestive of moyamoya disease or syndrome (MMD). We feel that the MMD in these patients was possibly caused, or exacerbated, by medications being used to control their cancer. The clinical need for the medications informed the management of MMD in these

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patients. Our experience suggests that stroke therapy should be tailored to these specific situations, which are pathologically different from the more common causes of intracranial stenosis and thrombo-embolism.

Case Reports

Case #1

A 63-year-old woman of European ancestry and a history of chronic myelogenous leukemia (CML) presented with right hemispheric ischemia. She had been treated with ponatinib, a tyrosine kinase inhibitor (TKI), for her CML for at least 2 years prior. TKIs used for CML treatment block the binding of ATP to the tyrosine kinase activated by the Philadelphia chromosome, BCR-ABL1, and stop uncontrollable cell growth.

Her imaging showed moderate bilateral middle cerebral artery (MCA) stenotic disease as well as moderate stenosis of the supraclinoid right internal cerebral artery (Fig 1, A). CT perfusion imaging demonstrated moderately elevated time to peak (TTP) in the right MCA territory, suggesting hypoperfusion (Fig 1, B). But she had suffered a fairly disabling stroke. In addition to changing her TKI to bosutinib (which has a more favorable vascular adverse-effect profile), and starting antiplatelet therapy, she underwent an indirect surgical bypass, encephalo-duro-arterio-synangiosis (EDAS), on the symptomatic right side. Her CML remained in remission. A follow-up catheter angiogram 7 months later showed stable steno-occlusive disease and a patent superficial temporal artery (STA) graft, but no flow to the brain via the graft. She has remained neurologically stable for a further 8 months, continuing with clopidogrel.

Case #2

A 48-year-old Filipina woman with a history of renal cell carcinoma presented with symptoms of right hemispheric ischemia. She had similar symptoms about 7 years earlier, and again a few months prior to presentation, with timely resolution. She was a smoker and had been on warfarin for about 4 years, for a deep venous thrombosis (DVT). There was a strong family history of cancer. The DVT was diagnosed at about the same time as the renal cell carcinoma. Cancer treatment included a nephrectomy, then a TKI, sunitinib. Her cancer had been under good control for about 4 years.

After diagnosing cerebrovascular disease, her sunitinib was stopped in consultation with her oncologist. She was convinced to decrease her smoking, though she would not quit completely. There was no evidence of residual DVT, so her warfarin was stopped and she was switched to aspirin. Both invasive and noninvasive imaging showed occluded bilateral MCAs and an occluded right anterior cerebral artery, but with excellent moyamoya-type deep collateral blood vessels (Fig 2, A). CT perfusion demonstrated hypoperfusion in the right MCA territory, with moderately elevated TTP (Fig 2, B).

A right EDAS procedure was done and she has remained symptom free. Follow-up angiography at 6 months showed improved caliber of the right proximal ACA (Fig 2, C). Modest flow through the graft to the brain (Perren Grade 2)[1] was demonstrated (Fig 2, D). In the short term she had no recurrence of her renal cell carcinoma, but she was diagnosed with a new type of

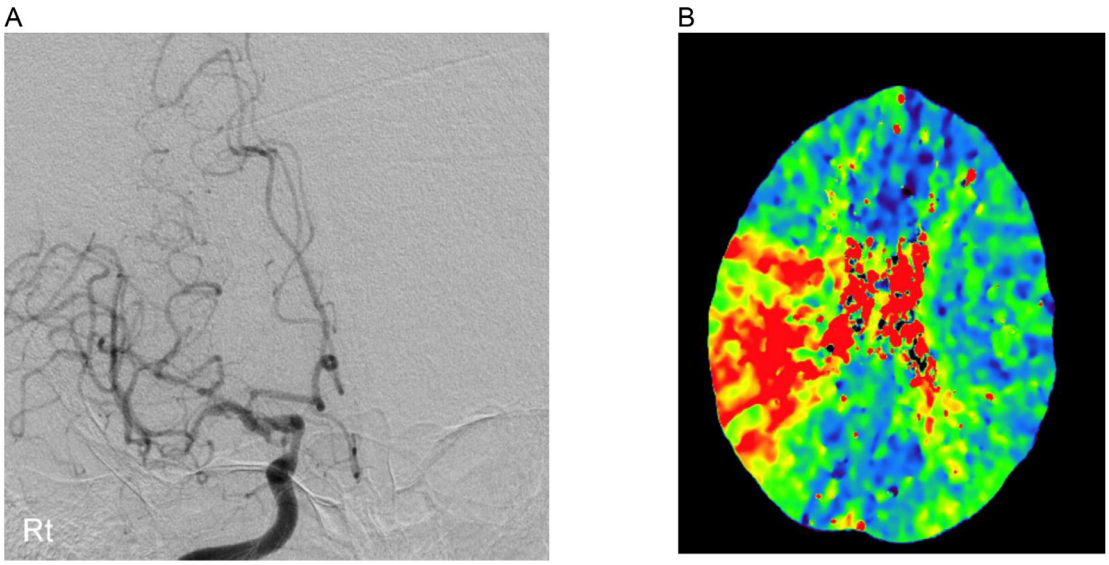

Figure 1. *(A) Right ICA angiogram, case #1: moderate stenoses of supraclinoid right ICA, MCA and ACA. (B) TTP CT perfusion image, case #1: marked delay in right MCA territory.*

carcinoma, originating from the breast. It was not certain if additional antineoplastic pharmacotherapy might end up being necessary for this individual.

Case #3

An 88-year-old Chinese man from Hong Kong with a diagnosis of metastatic hepatocellular carcinoma presented with an altered level of consciousness and diffuse subarachnoid hemorrhage (SAH). He had undergone a hepatectomy 17 years prior, and had been well until 6 months prior when he presented with diffuse peritoneal tumors, biopsy-confirmed to represent recurrent disease. Four months prior to the incident SAH, an experimental immunotherapy protocol had been started, with two mABs: bevacizumab and atezolizumab. Bevacizumab inhibits VEGF-A (an endothelial growth factor) and atezolizumab inhibits PD-L1 (programmed death ligand 1, which may be involved in the suppression of the immune response to neoplastic cells). His noninvasive imaging showed bilaterally occluded MCAs but no aneurysm or vascular malformation (Fig 3). It was felt that he probably bled from a dilated and fragile collateral artery. He was elderly, with a poor prognosis. He was treated conservatively and died about 5 days after admission. No autopsy was performed.

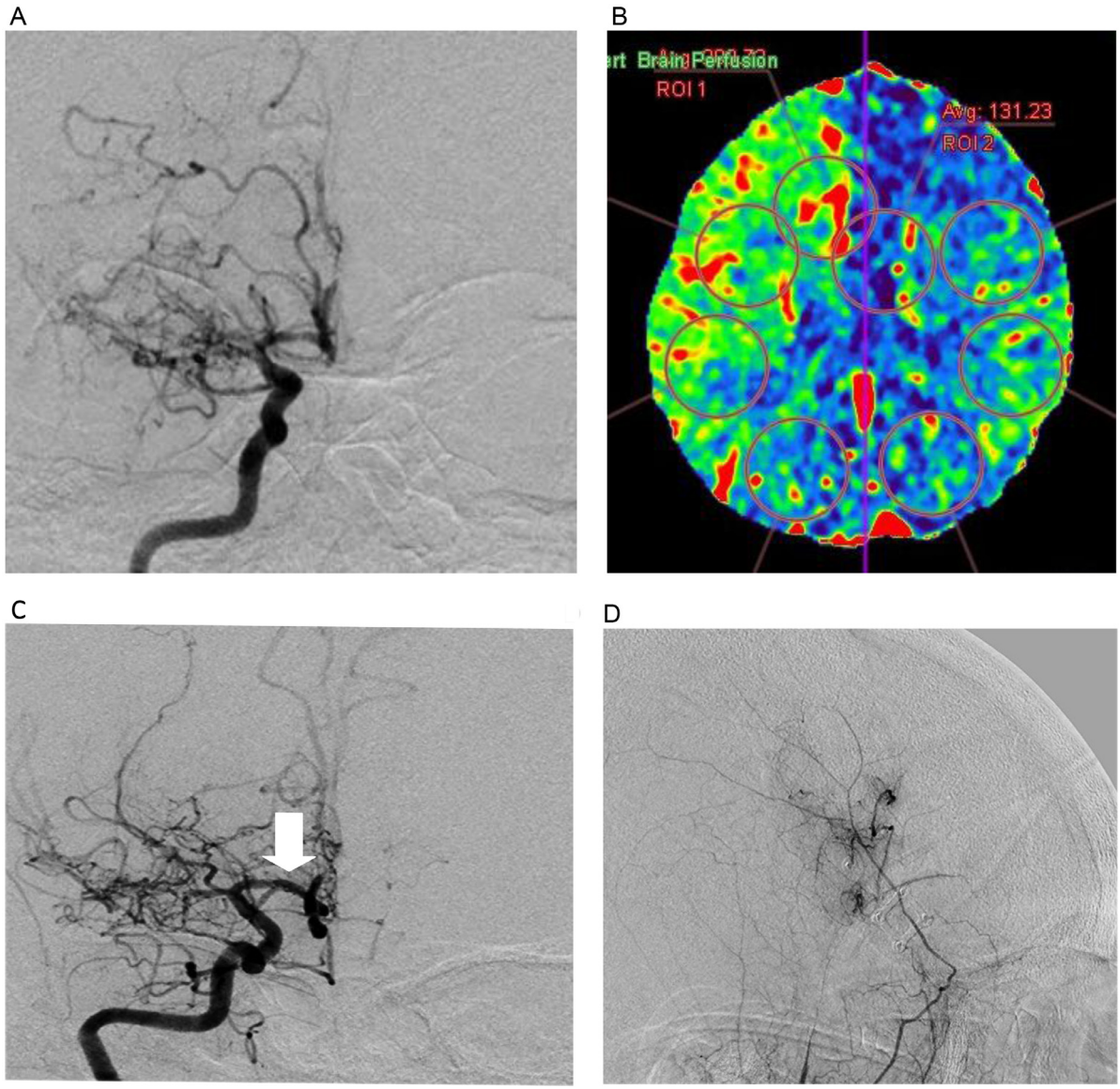

Figure 2. *(A) Right ICA angiogram, case #2: occlusion of right MCA with robust moyamoya-type collaterals, and stenotic disease in right ACA. (B) TTP CT perfusion image, case #2: marked delay in right MCA territory. (C) 6-month follow-up right ICA angiogram, case #2: persisting steno-occlusive disease in right MCA, but improved caliber of proximal right ACA (white arrow). (D) 6-month follow-up right ECA angiogram, case #2: moderate brain revascularization via STA graft demonstrated.*

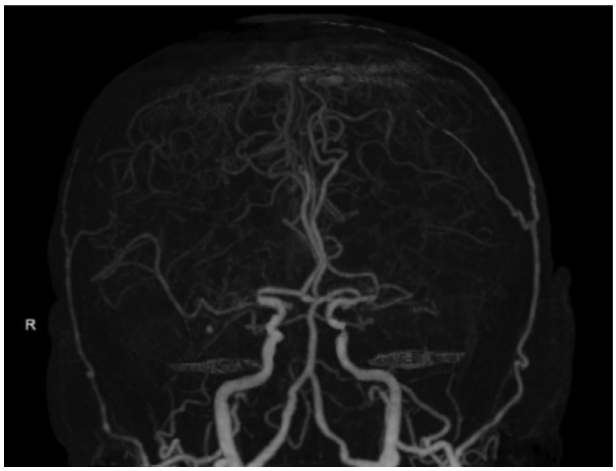

Figure 3. *CT angiogram, case #3: occluded bilateral MCAs, but no vascular malformation appreciated.*

Discussion

We cannot conclude that the observed intracranial occlusive disease was solely caused by our patients' cancer treatments. No cerebrovascular imaging antedating their strokes exists to prove or refute this point. However it is interesting that the first patient was not diabetic and did not appear to have any Asian ancestry despite the angiographic evidence of intracranial arterial stenoses. Perhaps these agents exacerbated pre-existing conditions, turning them from asymptomatic to symptomatic disease states?

A recent review of vascular toxicity associated with TKIs used to treat CML has reported that ponatinib, the initial CML treatment for case #1, has the greatest number of problems with vascular adverse events.[2] Indeed a phase I trial of ponatinib reported a 37% vascular adverse event risk, including stroke.[3] The one clinical case report linking a TKI to MMD described a patient, of Korean descent, on nilotinib (another TKI used for CML that has been identified as being more prone to vascular adverse events[3,4]). These CML TKI treatments are not always benign. Adverse vascular events may be explained by off-target effects, on other tyrosine kinase receptors, which may promote atherosclerosis and vascular toxicity.

Similar vascular problems, including stroke, have been reported with TKIs that are aimed at VEGF receptors as well.[5] Sunitinib, which was the initial treatment for case #2's renal cell carcinoma, is one of these drugs.

There is a well-established association between bevacizumab, the mAB aimed at VEGF-A, and cerebrovascular events, including occlusive cerebrovascular disease.[6] While our case #3 had an SAH, it seems unlikely that bevacizumab was the sole cause of his intracranial steno-occlusive disease; however it is possible that his occlusive disease was worsened by this agent and that increased stress on the collateral vessels caused the hemorrhage.

The superiority of direct versus indirect bypass in the treatment of chronic cerebrovascular insufficiency, including MMD has not been established. There remain proponents for both therapies. While surgeon experience and preference may dictate the decision making in many instances, the clinical situation must always be considered. Successful direct bypass procedures result in immediate and potentially more robust flow augmentation, which is necessary at times, especially when an acute deconstruction of the upstream angioarchitecture is planned. In situations of chronic, compensated ischemia, indirect bypasses may be of advantage in that they do not cause sudden shifts in flow dynamics to existing vessels. If the brain is ischemic enough collaterals do usually develop, presumably owing to the elaboration of angiogenic factors in the brain.

It is possible that our first case did not develop any collateral flow to the brain via her transposed superficial temporal artery/EDAS vessel because her brain did not have a perfusion deficit sufficient to promote the formation of collaterals. Unlike case #2 and #3, her MCA was not occluded. Her angiographic findings were not overwhelming, with only moderate degrees of intracranial arterial stenosis and perfusion abnormalities. An alternative hypothesis as to why her operation did not provide new flow to the brain is that her new TKI interfered with angiogenesis. If we had been able to stop the TKI completely, it might have changed the angiogenic milieu, and allowed for the EDAS to work. Alternatively, the change of TKI might have caused some regression of the occlusive disease, not demonstrable on follow-up angiography. The newer agent had a better side-effect profile in terms of vascular events.

Our case #2 stabilized clinically, perhaps in part due to discontinuation of her TKI. Indeed the follow-up angiogram here demonstrated regression of the stenosis in the proximal right ACA. She also showed some revascularization with the EDAS. The revascularization may have been less than robust due to her continued tobacco dependency, or perhaps due to regression of the cerebral arterial steno-occlusive disease after stopping the TKI. We can only guess what might have happened if she had continued on the TKI. There remains the ongoing issue of her new cancer, which may require future pharmacologic management.

If medications with potentially antiangiogenic properties need to be continued on a patient with cerebrovascular disease being considered for revascularization, perhaps direct bypass is a better choice. It is of interest that the one case report of a TKI-MMD association, though not compelling in terms of the association between the two entities, did report successful revascularization with direct bypasses.[4] The rationale for direct over indirect bypass here would be the interference in the development of new collaterals by a medication with antiangiogenic effects.

No comment can be made on the feasibility of a revascularization procedure or medication change in case #3 as he was elderly and with a very poor prognosis from his advanced cancer. It was decided to not treat this individual aggressively, and he died soon after presentation.

Conclusions

Stroke may be etiologically related to therapies for the chronic management of cancer in selected patients. While standard stroke treatments, including statins, antiplatelet/coagulant agents and antihypertensives, may be indicated, consideration should be given to the possibility that an agent being given to control the cancer might be involved in the genesis of the stroke. In these situations, stopping or changing the agent, after consultation with the oncologist may be warranted.

In cases where intracranial stenotic disease, such as MMD, is being considered for surgical treatment with a revascularization procedure, direct as opposed to indirect bypass may be a better option when treatment with a potentially vasotoxic agent needs to be continued. It is possible, however, that simply changing the medication to one with a better vascular adverse-event profile might stabilize and indeed lower the risk of further events and obviate the need for surgery.

The bottom line is that many cancer patients today have treatments that are associated with elevated risks of cerebrovascular adverse events. Careful clinical analysis, including the medication list, may lead to novel solutions beyond what have been generally entertained in the setting of acute stroke in this population.

Conflict of Interest

The authors declare no conflicts of interest.

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