

Risk of recurrent thromboembolic phenomena after ischemic stroke in patients with malignancy

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In the 1860s, Trousseau first described the association between cancer and a hypercoagulable state.¹ Ironically, he later diagnosed himself with phlebitis and predicted his own death from pancreatic cancer. Secretion of procoagulants by tumor cells, vascular damage secondary to immune response, and iatrogenic injury from chemotherapeutic agents, radiotherapy, and in-dwelling catheters, among other mechanisms, may contribute to hypercoagulability in the setting of cancer.² This places oncology patients at high risk of cerebrovascular phenomena, which frequently leads to patients' initial diagnosis.³ Despite this well-defined risk in patients with cancer, the incidence of recurrent thromboembolism and its effect on overall survival have received little attention.⁴

In the current issue of *Neurology*®, Navi et al.⁵ assess the characteristics of recurrent thromboembolic events after ischemic stroke in patients with cancer. They reviewed records of patients with cancer who had been diagnosed with acute ischemic stroke at Memorial Sloan-Kettering Cancer Center (MSKCC). Of the 263 patients, lung (32%) was the most common site of malignancy, adenocarcinoma (60%) was the most common tumor type, and the majority of patients had metastatic disease (69%). Median time from diagnosis of underlying cancer to index stroke was 9.7 months, but initial stroke occurred within 1 month of cancer diagnosis in 12%.

The authors found a median survival from index stroke of 84 days (interquartile range 24–419). Ninety patients (34%) had 117 recurrent thromboembolic events, consisting of 57 cases of venous thromboembolism, 36 recurrent ischemic strokes, 13 myocardial infarctions, 10 cases of systemic embolism, and one TIA. Kaplan-Meier rates of recurrent thromboembolism were 21%, 31%, and 37% at 1, 3, and 6 months, respectively, and cumulative rates of recurrent ischemic stroke were 7%, 13%, and 16%.

Stroke and cancer represent major causes of disability and death, and both conditions predispose to an increased risk of thromboembolic phenomena. Thus, it is surprising that this area has not received further attention. The authors demonstrate that patients with acute ischemic stroke in the setting of

active cancer face a substantial short-term risk of recurrent ischemic stroke and thromboembolism. The stroke recurrence rates exceed those found in patients known to be at particularly high risk of recurrent stroke and are 3 times those found in recent trials.^{6,7}

Further studies must determine the precise etiology of primary and recurrent strokes in these patients. Surprisingly, confirmed etiology of initial strokes from cancer-related hypercoagulable mechanisms such as nonbacterial thrombotic endocarditis and disseminated intravascular coagulation were uncommon (5%). Although unconfirmed in the majority of cases, nonbacterial thrombotic endocarditis (NBTE) presumably accounts for many of the recurrent strokes. Prior autopsy studies demonstrated that NBTE is a primary cause of ischemic stroke in patients with cancer.⁸

Risk stratification measures are also necessary for prognosis and to optimize specific therapeutic algorithms. Although only adenocarcinoma independently predicted recurrent thromboembolic phenomena, the authors found more recurrent events in patients with NBTE and recent chemotherapy, but this did not reach statistical significance, perhaps because of a type II error and inadequate power. Patients treated with multimodal adjuvant therapies are particularly at risk of ectopic fat, dyslipidemia, insulin resistance, and hypertension, all of which may increase the risk of recurrent thromboembolic events, particularly cardiac and cerebral thrombosis.⁹ Radiation also may directly lead to cardiac valvular disease, peripheral vascular disease, and stroke. These patients have many additional iatrogenic and noniatrogenic risk factors for stroke.

In the present study, median modified Rankin Scale score at hospital discharge was 3 (interquartile range 2–5) with the majority of patients discharged home (56%). Recurrent thromboembolism was associated with increased mortality. In addition, recurrent stroke accounted for 31% of all thromboembolic events, likely leading to substantial morbidity and mortality. Further studies are indicated to determine how recurrent thromboembolic events affect overall

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functional outcome, because decreased patient mobility greatly increases the risk of recurrent events.

Perhaps the greatest area of improvement may be in the development of patient- and disease-specific diagnostic and therapeutic approaches. In the current study, evaluations were not standardized; 24% of patients did not have vessel imaging and 16% did not have echocardiography. In addition, optimal therapies in these patients are currently unclear. It was speculated that additional thromboprophylaxis in patients with cancer may improve quality of life and prognosis, but, at present, outpatient prophylaxis is not supported by national guidelines.¹⁰ A phase 3 randomized trial to determine the benefits of primary stroke prevention in patients with high venous thromboembolism risk is currently ongoing (clinicaltrials.gov identifier NCT00876915). Patients with a history of ischemic stroke or thromboembolic events are often managed with antiplatelet agents or anticoagulation. In the current study, there was no difference in recurrent thromboembolism or death between groups receiving antiplatelet vs anticoagulant therapy. It is possible that patients with history of cancer and stroke may benefit particularly from more aggressive prophylactic strategies.

The current study has a number of limitations, many of which are well discussed by the authors. MSKCC is an urban, tertiary-care hospital specializing in the care of patients with cancer, but is not a primary stroke center. Thus, many cases of acute stroke or thromboembolic events may not have been treated at MSKCC, leading to an underestimation of the actual risk and morbidity or mortality of thromboembolic events.

Despite these limitations, this is an important study. Lingering questions regarding the risk of recurrent thromboembolic events, the most appropriate diagnostic modalities, and optimal therapeutic management in patients with cancer and a history of stroke will undoubtedly be further addressed by the relevant, ongoing randomized clinical trial (clinicaltrials.gov identifier NCT01763606). The authors should be commended for highlighting this

important subject because it underscores the risk of recurrent thromboembolic events in these patients and will help define the most appropriate management strategies.

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