Case Studies

Antithrombotic Therapy Strategy for Cancer-Associated Ischemic Stroke: A Case Series of 26 Patients

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Background: The risk of complications from thromboembolism is increased for patients with malignancy. Cancer-associated stroke is also a serious issue with regard to the management of patients with cancer because stroke incidence often causes disabilities that affect daily life and cancer treatment strategy. *Methods:* Between March 2011 and September 2017, 328 patients with acute ischemic stroke were registered to our hospital. *Results:* Of these patients, 26 (7.9%) had a cancer-associated stroke diagnosis, namely, Trousseau syndrome. After ischemic stroke onset, malignancy treatment was changed to palliative treatment for 11 patients. Eighteen patients died 1 year after ischemic stroke onset, and 15 of these patients underwent cancer treatment according to the best supportive care policy. Of those who died, 8 underwent anticoagulation therapy. We described the clinical courses of 3 cases among 26 cases with Trousseau syndrome. Two cases took direct oral anticoagulants (DOACs) due to cancer-associated venous thromboembolism before stroke onset, and there has been no stroke recurrence with subcutaneous unfractionated heparin. In the third case, when cancer activity was suppressed, we changed DOACs from subcutaneous unfractionated heparin and continued DOACs without thromboembolic events. *Conclusions:* There is insufficient evidence regarding cases for which DOACs would be suitable for the prevention of thromboembolism and regarding its long-term efficacy and safety in patients with cancer. As it stands, heparin treatment, which has multifaceted antithrombotic actions, may be suitable for cancer-associated stroke prevention. **Key Words:** Acute ischemic stroke—Trousseau syndrome—venous thromboembolism—heparin—direct oral anticoagulants.

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Introduction

The risk of complications due to thromboembolism is increased for patients with malignancies. Thromboembolism is the second leading cause of death for patients with cancer, followed by death from cancer itself.[1] Venous thromboembolism (VTE) such as deep venous thrombosis (DVT) is a frequent complication in these patients.[2] In addition, their incidence of arterial thrombosis is 4.7%, which is 2 times higher than that of patients without cancer.[3] Trousseau syndrome often refers to a hypercoagulation disorder related to malignant tumors or general arteriovenous thrombosis resulting from malignant tumors.[4] Cancer-associated stroke is also a serious issue associated with the management of patients with cancer because stroke incidence often causes disabilities that affect daily life and influences cancer treatment strategy. In addition, cancer-associated stroke has been considered as one of the etiologies of a cryptogenic stroke.[5] Cancer-associated stroke is associated with complicated pathological conditions because it can cause both venous and arterial thrombi, such as nonbacterial thrombotic endocarditis (NBTE).[4] Therefore, it is necessary to determine whether a venous or arterial thrombus caused the ischemic stroke when selecting antithrombotic drugs for secondary prevention. However, the effects of antithrombotic drugs for preventing recurrence of cancer-associated stroke have not been established. Here, we present the clinical features of patients with acute ischemic stroke due to Trousseau syndrome and describe the clinical courses of several cases. We also discuss antithrombotic treatment for patients with cancer-associated stroke.

Clinical Characteristics of Patients with Cancer-Associated Stroke

Between March 2011 and September 2017, 328 patients with acute ischemic stroke were admitted to our hospital. Stroke subtypes were classified according to the criteria laid down by the Trial of ORG 10172 in Acute Stroke Treatment classification.[6] We excluded patients with conventional mechanisms (large artery atherosclerosis, small vessel occlusion, and cardioembolism). In addition, stroke patients, due to other determined etiology (arteritis, dissection, migraine/vasospasm, drug misuse, and so on), were excluded. Patients who had undetermined etiology stroke and suffered from active cancer were diagnosed with cancer-associated stroke. Active cancer was defined as a new diagnosis, treatment, and progression within the prior 6 months or known recurrence or metastasis.[7,8] Patients with primary brain tumors were excluded. As a result, 26 patients (7.9%) were diagnosed as having cancer-associated stroke, namely, Trousseau syndrome. Clinical features of patients with acute ischemic stroke are shown in Table 1. There were 18 patients (69.2%) with stage IV cancer according to the tumor, node, metastasis classification. There were 14 cases of adenocarcinoma among 24 patients with pathological findings (58.3%). Three cases were found to be malignant after the onset of ischemic stroke. Eighteen patients underwent active treatment for malignancy at the onset of ischemic stroke. Four patients followed the policies of best supportive care (BSC). The D-dimer values were elevated in all cases. In our study, 4 patients (15.4%) were diagnosed with NBTE. After ischemic stroke onset, malignancy treatment was switched to palliative treatment in 11 patients. Twenty-three patients died during the follow-up period. Eighteen patients died 1 year after ischemic stroke onset, and 15 of them underwent cancer treatment according to the BSC policy. Of those who died, 8 underwent anticoagulation therapy (warfarin for 4, intravenous unfractionated heparin for 1, subcutaneous unfractionated heparin for 1, apixaban for 1, and edoxaban for 1), 1 was administrated aspirin, and 9 were not administrated any antithrombotic agent. Of 7 patients with cerebrocardiovascular events (4 with ischemic stroke, 1 with cerebral hemorrhage, 1 with angina pectoris, and 1 with aortic dissection), 5 died within 1 year.

Case Presentation

Case 1. A Patient Presented with Ischemic Stroke while Taking Edoxaban for DVT and Repeated Warfarin-Resistant DVT

A 66-year-old man was referred to our hospital for dysphagia and left-hand clumsiness. Lung adenocarcinoma with bone metastasis was diagnosed 3 years ago, and he was administered with gefitinib after surgical resection of the lung tumor. He was administered edoxaban (60 mg daily), since DVT was diagnosed based on an increased D-dimer level (10.2 μg/mL) and evidence of thrombi in his right popliteal vein was seen through ultrasound examination and contrast-enhanced computed tomography (CT) 2 weeks before hospitalization. Although ultrasound examination of the lower extremities on admission showed no thrombi, brain magnetic resonance imaging (MRI) showed multiple acute infarctions in the right occipital lobe, bilateral anterior lobe, bilateral parietal lobe, and bilateral cerebellar hemisphere (Fig 1, A,B). Transesophageal echocardiography showed no remarkable findings, such as NBTE, right-to-left shunt, and aortic arch thrombus. An undetermined cerebral infarction with malignancy led us to suspect Trousseau syndrome. Therefore, we started both intravenous unfractionated heparin and warfarin treatment. Due to the patient's independence in performing activities of daily living, we discontinued heparin after the prothrombin time international normalized ratio was in the therapeutic range (2-3). However, acute-onset DVT developed repeatedly after changing the antithrombotic treatment to warfarin alone. We took into consideration that the patient had