Abstract. – OBJECTIVE: It is still unknown whether early tirofiban treatment improves prognosis in patients with cancer-related ischemic stroke without intravenous thrombolytic therapy. The purpose of this study was to assess the safety and efficacy of tirofiban in patients with cancer-associated ischemic stroke.

PATIENTS AND METHODS: A retrospective analysis was performed on 75 patients with cancer and mild to moderate ischemic stroke, 34 of whom received tirofiban treatment and 41 aspirin treatment. The aspirin group received aspirin 100 mg QD, while the tirofiban group received continuous intravenous administration of tirofiban at a dosage of 0.1 μg/kg/min for 48 hours before switching to oral aspirin.

RESULTS: The 24-hour and 7-day National Institute of Health Stroke Scale (NIHSS) scores for the tirofiban group were lower than those for the aspirin group (p=0.017 and p=0.035, respectively). The proportion of intracerebral hemorrhage occurring within 7 days did not differ significantly between the two groups (p=0.05), and neither did the 90-day Modified Rankin Scale (mRS) scores nor the incidence of ischemic stroke.

CONCLUSIONS: Early administration of tirofiban in the treatment of mild to moderate ischemic stroke is safe, which can reduce 24-hour and 7-day NIHSS scores and has potential value.

Key Words: Ischemic Stroke, Cancer, Tirofiban, Aspirin.

Introduction

With a prevalence of 25-30% in the population, ischemic stroke has a high rate of morbidity and disability. Previously, it was a common practice to ignore ischemic stroke related to cancer. Approximately 40% of all human beings will have a malignancy during their lifetimes. As the population ages and cancer patients live longer, the comorbidity of tumor and ischemic stroke occurs more frequently, with a statistical incidence of 4-20%1,5. Long-term quality of life is becoming increasingly important for cancer patients as tumor detection and therapy improve, but cancer-related ischemic stroke remains the leading cause of death and disability. Therefore, it is crucial to research tumor therapy strategies in conjunction with ischemic stroke.

Currently, there is confusion over whether patients with cancer-related ischemic stroke should receive the same care as those who do not have tumor complications or whether they should be treated differently according to a new subtype. Intravenous rt-PA thrombolytic therapy within 4.5 hours after symptom onset is safe and effective in treating patients with cancer-associated ischemic stroke, and previous research suggests similar safety and effectiveness compared to patients without tumor combination. No consensus has been reached regarding the best course of treatment for patients with cancer-associated ischemic stroke who do not have non-intracranial large artery occlusion and miss the window of opportunity. Tirofiban is a non-peptide glycoprotein IIb/IIIa platelet receptor antagonist that is highly selective, fast-acting, and in addition to being FDA-approved to treat acute coronary syndromes. Numerous clinical trials and meta-analysis have shown that the administration of tirofiban does not increase the risk of a cerebral hemorrhage in patients with ischemic stroke, which may be advantageous. However, in earlier studies on tirofiban for the treatment of ischemic stroke, patients with tumor complications were not examined as an independent study object. Tirofiban is frequently used by doctors in China’s actual clinical settings these days to consider treating ischemic stroke patients who
have lost the window of opportunity. Tirofiban is therefore used to treat a significant portion of ischemic stroke cases in China. We performed a retrospective study to examine the safety and effectiveness of tirofiban in patients with cancer-related ischemic strokes.

**Patients**

This retrospective study included 75 patients who were hospitalized at Chenghai District People’s Hospital between February 01, 2018, and June 30, 2022. Inclusion criteria were: 1. Patients with ischemic stroke without intravenous thrombolysis within 24 hours of onset; 2. Non-intracranial large vessel occlusion confirmed by computed tomography angiography; 3. Diagnosis of malignant tumor; 4. Mild to moderate ischemic stroke; 5. Age 18 and above. Exclusion criteria were: 1. Hypothrombocytopenia (platelet concentration <100×10⁹/L); 2. Primary intracranial tumors or brain metastases; 3. History of intracranial hemorrhage within 3 months. Malignancy was defined as any systemic cancer that has been definitively diagnosed or treated; Acute ischemic stroke was defined as any new neurological impairment with corresponding evidence of acute ischemic magnetic resonance imaging (MRI). Mild to moderate ischemic stroke was defined as an NIHSS score of 4-15.

**Treatment Methods and Observation Indicators**

The aspirin group received aspirin 100 mg QD, while the tirofiban group received continuous intravenous administration of tirofiban at a dose of 0.1 μg/kg/min for 48-hour before switching to oral aspirin. The following details were collected: demographic information, complications, medication regimen, tumor type and stage, tumor therapy, NIHSS score, mRS score, ischemic stroke recurrence, and other indicators. Ischemic stroke recurrence was defined as a new focal neurological deficit with MRI showing a new cerebral infarct lesion. The hospital’s ethics committee approved the study.

**Statistical Analysis**

Continuity variables were described by mean±standard deviation, and statistical analysis was performed by t-test of two independent samples. Categorical variables were described using percentages or rates, and rank variables were analyzed using the Chi-square or Fisher’s exact test. The statistical software SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for the analysis. p<0.05 was considered to be statistically significant.

**Results**

**Information**

Except for the proportion of smokers in the tirofiban group, which was higher than that in the aspirin group, there were no statistically significant differences in age, gender, complications, and pre-onset NIHSS score between the two groups, as shown in Table I.

**NIHSS Score and Complications**

The 24-hour NIHSS score of the tirofiban group was 7.00±2.93 points and 6.06±3.16 points on day 7; the 24-hour NIHSS score of the aspirin group was 8.80±3.78 points and 7.68±3.34 points on day 7. Moreover, at 24-hour and 7-day, the NIHSS score of the tirofiban group was lower than that of the aspirin group. As shown in Figure 1, the difference was statistically significant (24-hour: p=0.017; 7-day: p=0.035).

Within 7 days, 5 patients (6.67%) developed cerebral hemorrhage transformation, 2 patients (5.88%) in the tirofiban group, including 1 case of symptomatic cerebral hemorrhage, and 3 patients (7.31%) in the aspirin group, including 1 case of a symptomatic cerebral hemorrhage. There was no significant difference in the conversion ratio of cerebral hemorrhage between the two groups (p=1.000). Within 7 days, neither group experienced a fatality nor significant systemic bleeding.

**mRS Score at 90-Day and Ischemic Stroke Recurrence Rate**

The 90-day mRS scores (mRS 0-2) indicated a favorable prognosis for 56% (20 of 34) of the tirofiban group and 53% (22 of 41) of the control group, with no statistically significant difference between the two groups (p=0.656), as shown in Figure 2. Three patients in the tirofiban group experienced an ischemic stroke with a recurrence rate of 8.82%, while four patients in the aspirin group experienced a new ischemic stroke with a recurrence rate of 9.76%, showing no statistical difference between the two groups (p=1.000).
Discussion

As compared to aspirin, tirofiban treatment reduced the 24-hour and 7-day NIHSS scores in patients with cancer-associated ischemic stroke while not raising the risk of cerebral hemorrhage, according to the current retrospective case study. To the best of our knowledge, this is the first case report of tirofiban therapy for patients who experienced both an ischemic stroke and a tumor.

Tumors and ischemic stroke share many risk factors, such as aging, obesity, smoking, etc. However, the incidence of ischemic stroke increases in patients with tumors compared with those without tumors, indicating that one risk factor for ischemic stroke is the tumor itself.

Embolization is one of the mechanisms cause cancer complicated with ischemic stroke. Moreover, advanced malignancies may cause disseminated intravascular coagulation that can lead to ischemic cerebrovascular events. Prior anticoagulant therapy did not show any additional advantages over antiplatelet therapy in the management of ischemic stroke in conjunction with tumors. The ischemic stroke recurrence rate was the same for anticoagulant therapy and antiplatelet therapy in a retrospective cohort analysis of 263 patients with tumor combination ischemic stroke. In a recent prospective randomized controlled trial (TEACH) comparing low molecular weight heparin and aspirin for the treatment of cancer-associated ischemic stroke. Enrollment failure due
Tirofiban and cancer-associated ischemic stroke

To patient aversion to prolonged subcutaneous injections resulted in the study’s premature termination, and no significant advantage of low molecular weight heparin over aspirin was found in the 1-year follow-up of enrolled patients. In the subgroup analysis of NAVIGATE embolic stroke of undetermined source (ESUS) randomized trials, ischemic stroke recurrence rates in patients with cancer associated ESUS type stroke were 7.7% in the rivaroxaban and 5.4% in the aspirin group, with no difference between the two groups.

Platelet hyperfunction is present in patients with cancer-associated ischemic stroke, although atherosclerosis continues to be a major factor in cancer-related ischemic stroke. Therefore, antiplatelet therapy for cancer-associated ischemic stroke is theoretically effective. Recently, tirofiban has been tested in the treatment of ischemic stroke. Tirofiban is safe for patients with moderate ischemic stroke, according to the SaTIS trial. In addition, there is no proof that using tirofiban in combination with alteplase or endovascular mechanical thrombectomy increases the risk of intracerebral hemorrhage in people who have had an ischemic stroke. Tirofiban significantly improved the 90-day mRS score and NIHSS score compared to conventional aspirin, according to a recent multicenter, randomized clinical trial (ESCAPIST Trial) for the treatment of mild to moderate ischemic stroke. When compared to aspirin alone, tirofiban treatment had lower NIHSS scores in our group of cases 24 hours and 7 days after the onset of the condition, but no improvement in 90-day mRS scores was seen.

In a prospective trial, 74 patients with cancer and acute ischemic stroke had micro emboli found on transcranial doppler (TCD) ultrasound in nearly half of them. Tirofiban, which is an antagonist of the IIb/IIIa platelet receptor, has been demonstrated in two earlier TCD monitoring studies of carotid artery exfoliation to significantly lessen the micro-emboli of carotid artery exfoliation. This may account for tirofiban’s superior short-term symptomatic relief compared to aspirin alone in patients with cancer-associated ischemic stroke. The rate of ischemic stroke recurrence in this group of cases did not differ between aspirin and short-term tirofiban therapy. The failure to observe a decrease in the rate of ischemic stroke recurrence and the 90-day mRS good prognosis rate with tirofiban in this group of cases may also be explained by this. The prognosis and recurrence rates currently seen in patients with cancer-associated ischemic stroke may be highly correlated with these outcomes.

Limitations
Bias may exist due to the retrospective single-center nature of the present study, which only included a few cases. The small number of patients prevented us from conducting a stratified investigation on the relationship between tumor stage and treatment strategy. We believe that future prospective clinical studies will strengthen this evaluation.

Conclusions
Treatment with tirofiban for cancer-related ischemic stroke reduced 24-hour and 7-day NIHSS scores while not raising the risk of bleeding.
Acknowledgements
We thank Dr Gengzhen CHEN for data requirement.

Ethics Approval
The local Ethical Committee approved the study protocol (People’s Hospital of Chenghai Shantou Ethics Committee), which was carried out under the principles of the Declaration of Helsinki (No.: 20220610 V2.0; Date: 2022.06.10).

Informed Consent
Written informed consent was obtained from all patients who accepted to participate in the study.

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest
The authors reported no potential conflict of interest.

Funding
No specific funding from public, commercial, or profit funding agencies was received.

Authors’ Contributions
Guolian Zhu made contributions to the study conception and design, Zemin Zhang contributed to drafting the manuscript, Zehuai Lin contributed to analysis and interpretation of data. All authors read and approved the final manuscript.

ORCID ID
Zemin Zhang: 0000-0003-0002-5040
Zehuai Lin: 0000-0002-2353-2101
Guolian Zhu: 0000-0002-9344-5660

References
Tirofiban and cancer-associated ischemic stroke


