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Tirofiban in the treatment of cancer-associated ischemic stroke

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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:
Alschemic Stroke, Cancer, Tirofiban, Aspirin.

Introduction

With a prevalence of 25-30% in the population, ischemic stroke has a high rate of morbidity and disability[1]. 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[2]. 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%[3-5]. 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[6]. 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[7]. 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[8] 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[9]. Numerous clinical trials[10-16] 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[10-16] 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

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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 and Methods

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. Hypo thrombocytopenia (platelet concentration $<100\times10^9$/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.

The 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 ($p=1.000$).

Table I. Baseline characteristics.

	Tirofiban (n=34)	Aspirin (n=41)	t/χ^2	*p*-value
Age, years, mean (sd)	67.91 (10.10)	65.24 (7.92)	1.282	0.204
Gender				
Male, No. (%)	25 (73.53)	31 (75.61)	0.043	0.837
Female, No. (%)	9 (26.47)	10 (24.39)		
Smoking, No. (%)	19 (55.88)	10 (24.39)	9.027	0.003
Atrial fibrillation, No. (%)	6 (17.65)	9 (21.95)	0.215	0.643
Hyperlipidemia, No. (%)	19 (55.88)	23 (56.10)	0.001	0.985
Diabetes, No. (%)	16 (47.06)	17 (41.46)	0.236	0.627
Hypertension, No. (%)	27 (79.41)	29 (70.73)	0.740	0.390
Cancer type				
Solid tumor, No. (%)	30 (88.24)	37 (90.24)	0.079	0.779
Hematologic tumor, No. (%)	4 (11.76)	4 (9.76)		
Metastatic cancer, No. (%)	21 (61.76)	21 (51.22)	1.280	0.258
Radiation therapy No. (%)	3 (8.82)	9 (21.95)	2.383	0.123
Chemical therapy, No. (%)	9 (26.47)	19 (46.34)	3.137	0.077
NIHSS score, mean (sd)	6.85 (2.57)	7.95 (2.99)	1.685	0.096
Symptom onset-to-inclusion interval, h, mean (sd)	12.35 (5.81)	12.76 (4.53)	0.330	0.737
ASPECTS, mean (sd)	8.79 (0.91)	8.44 (1.10)	1.504	0.137

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[17], 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[18].

Embolization is one of the mechanisms cause cancer complicated with ischemic stroke[19]. Moreover, advanced malignancies may cause disseminated intravascular coagulation that can lead to ischemic cerebrovascular events[20]. 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 stroke21. In a recent prospective randomized controlled trial (TEACH)[22] comparing low molecular weight heparin and aspirin for the treatment of cancer-associated ischemic stroke. Enrollment failure due

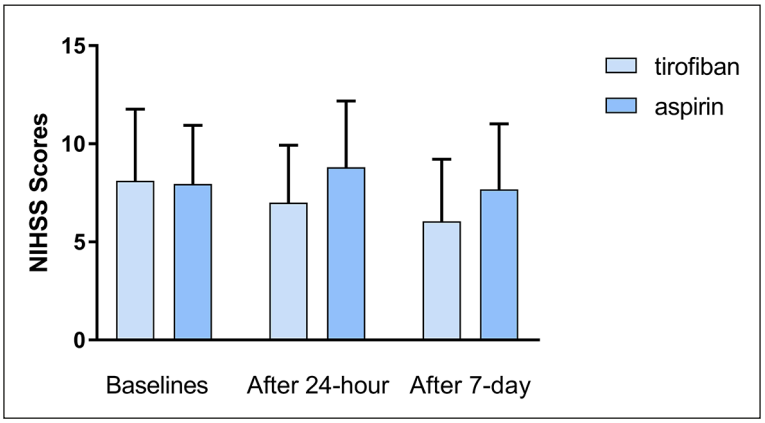

Figure 1. The NIHSS scores change at 24-hour and 7-day.

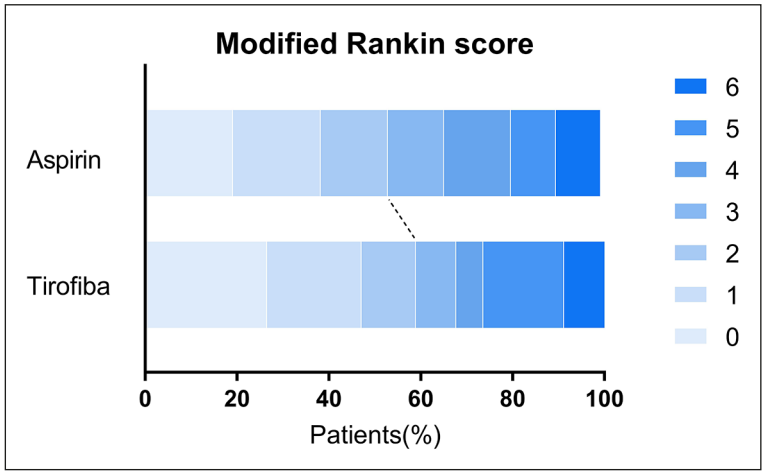

Figure 2. Distribution of the mRS scores at 90 days.

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[23], 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[24-26], although atherosclerosis continues to be a major factor in cancer-related ischemic stroke[27]. 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[10]. 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[28-30]. Tirofiban significantly improved the 90-day mRS score and NIHSS score compared to conventional aspirin, according to a recent multicenter, randomized clinical tria[l14] (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[31], 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[32,33] 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[21].

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.

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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.

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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.

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References

1) White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. Am J Prev Med 2014; 46: S7-S15.
2) GBD 2016 Lifetime Risk of Stroke Collaborators, Feigin VL, Nguyen G, Cercy K, Johnson CO, Alam T, Parmar PG, Abajobir AA, Abate KH, Abd-Allah F, Abejie AN, Abyu GY, Ademi Z, Agarwal G, Ahmed MB, Akinyemi RO, Al-Raddadi R, Aminde LN, Amlie-Lefond C, Ansari H, Asayesh H, Asgedom SW, Atey TM, Ayele HT, Banach M, Banerjee A, Barac A, Barker-Collo SL, Bärnighausen T, Barregard L, Basu S, Bedi N, Behzadifar M, Béjot Y, Bennett DA, Bensenor IM, Berhe DF, Boneya DJ, Brainin M, Campos-Nonato IR, Caso V, Castañeda-Orjuela CA, Rivas JC, Catalá-López F, Christensen H, Criqui MH, Damasceno A, Dandona L, Dandona R, Davletov K, de Courten B, deVeber G, Dokova K, Edessa D, Endres M, Faraon EJA, Farvid MS, Fischer F, Foreman K, Forouzanfar MH, Gall SL, Gebrehiwot TT, Geleijnse JM, Gillum RF, Giroud M, Goulart AC, Gupta R, Gupta R, Hachinski V, Hamadeh RR, Hankey GJ, Hareri HA, Havmoeller R, Hay SI, Hegazy MI, Hibstu DT, James SL, Jeemon P, John D, Jonas JB, Jóźwiak J, Kalani R, Kandel A, Kasaeian A, Kengne AP, Khader YS, Khan AR, Khang YH, Khubchandani J, Kim D, Kim YJ, Kivimaki M, Kokubo Y, Kolte D, Kopec JA, Kosen S, Kravchenko M, Krishnamurthi R, Kumar GA, Lafranconi A, Lavados PM, Legesse Y, Li Y, Liang X, Lo WD, Lorkowski S, Lotufo PA, Loy CT, Mackay MT, Abd El Razek HM, Mahdavi M, Majeed A, Malekzadeh R, Malta DC, Mamun AA, Mantovani LG, Martins SCO, Mate KK, Mazidi M, Mehata S, Meier T, Melaku YA, Mendoza W, Mensah GA, Meretoja A, Mezgebe HB, Miazgowski T, Miller TR, Ibrahim NM, Mohammed S, Mokdad AH, Moosazadeh M, Moran AE, Musa KI, Negoi RI, Nguyen M, Nguyen QL, Nguyen TH, Tran TT, Nguyen TT, Anggraini Ningrum DN, Norrving B, Noubiap JJ, O'Donnell MJ, Olagunju AT, Onuma OK, Owolabi MO, Parsaeian M, Patton GC, Piradov M, Pletcher MA, Pourmalek F, Prakash V, Qorbani M, Rahman M, Rahman MA, Rai RK, Ranta A, Rawaf D, Rawaf S, Renzaho AM, Robinson SR, Sahathevan R, Sahebkar A, Salomon JA, Santalucia P, Santos IS, Sartorius B, Schutte AE, Sepanlou SG, Shafieesabet A, Shaikh MA, Shamsizadeh M, Sheth KN, Sisay M, Shin MJ, Shiue I, Silva DAS, Sobngwi E, Soljak M, Sorensen RJD, Sposato LA, Stranges S, Suliankatchi RA, Tabarés-Seisdedos R, Tanne D, Nguyen CT, Thakur JS, Thrift AG, Tirschwell DL, Topor-Madry R, Tran BX, Nguyen LT, Truelsen T, Tsilimparis N, Tyrovolas S, Ukwaja KN, Uthman OA, Varakin Y, Vasankari T, Venketasubramanian N, Vlassov VV, Wang W, Werdecker A, Wolfe CDA, Xu G, Yano Y, Yonemoto N, Yu C, Zaidi Z, El Sayed Zaki M, Zhou M, Ziaeian B, Zipkin B, Vos T, Naghavi M, Murray CJL, Roth GA. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. N Engl J Med 2018; 379: 2429-2437.
3) Wilbers J, Sondag L, Mulder S, Siegerink B, van Dijk EJ, Dutch String-of-Pearls Stroke Study Group. Cancer prevalence higher in stroke patients than in the general population: the Dutch String-of-Pearls Institute (PSI) Stroke study. Eur J Neurol 2020; 27: 85-91.
4) Kiyuna F, Sato N, Matsuo R, Kamouchi M, Hata J, Wakisaka Y, Kuroda J, Ago T, Kitazono T; Fukuoka Stroke Registry Investigators. Association of Embolic Sources with Cause-Specific Functional Outcomes Among Adults With Cryptogenic Stroke. JAMA Netw Open 2018; 1: e182953.
5) Sanossian N, Djabiras C, Mack WJ, Ovbiagele B. Trends in cancer diagnoses among inpatients hospitalized with stroke. J Stroke Cerebrovasc Dis 2013; 22: 1146-1150.

6) Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report from the American Heart Association. Circulation 2017; 135: e146-e603.

7) Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019; 50: e344-e418.

8) Huang S, Lu X, Tang LV, Hu Y. Efficacy and safety of intravenous thrombolysis for acute ischemic stroke in cancer patients: a systemic review and meta-analysis. Am J Transl Res 2020; 12: 4795-4806.

9) Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338: 1488-1497.

10) Siebler M, Hennerici MG, Schneider D, von Reutern GM, Seitz RJ, Röther J, Witte OW, Hamann G, Junghans U, Villringer A, Fiebach JB. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. Stroke 2011; 42: 2388-2392.

11) Tao C, Zhu Y, Zhang C, Song J, Liu T, Yuan X, Luo W, Chen C, Liu D, Zhu Y, Liu J, Hu W. Association between tirofiban monotherapy and efficacy and safety in acute ischemic stroke. BMC Neurol 2021; 21: 237.

12) Zhang H, Lin F, Zhao Y, Chang W, Liu H, Yin J, Li L. Assessing the Efficacy and Safety of Tirofiban in Combination with Dual-antiplatelet Therapy in Progressive Ischemic Stroke Patients. J Cardiovasc Pharmacol 2021; 78: 448-452.

13) Cai L, Yu X, Yu J, Xu J, Xu L, Ling C, Lou M, Yu C, Qian C. Can Tirofiban Improve the Outcome of Patients with Acute Ischemic Stroke: A Propensity Score Matching Analysis. Front Neurol 2021; 12: 688019.

14) Han B, Ma T, Liu Z, Wu Y, Tan W, Sun S, Li X, Shao C, Tang D, Sun J. Efficacy and Safety of Tirofiban in Clinical Patients with Acute Ischemic Stroke. Front Neurol 2022; 12: 785836.

15) Zhou J, Gao Y, Ma QL. Safety and efficacy of tirofiban in acute ischemic stroke patients not receiving endovascular treatment: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2020; 24: 1492-1503.

16) Du N, Wang LX, Liu YL, Yin XL, Zhao JS, Yang L. Effect of tirofiban in treating patients with progressive ischemic stroke. Eur Rev Med Pharmacol Sci 2022; 26: 2098-2105.

17) Woock M, Martinez-Majander N, Seiffge DJ, Selvik HA, Nordanstig A, Redfors P, Lindgren E, Sanchez van Kammen M, Rentzos A, Coutinho JM, Doyle K, Naess H, Putaala J, Jood K, Tatlisumak T. Cancer and stroke: commonly encountered by clinicians, but little evidence to guide clinical approach. Ther Adv Neurol Disord 2022; 15: 17562864221106362.

18) Navi BB, Howard G, Howard VJ, Zhao H, Judd SE, Elkind MSV, Iadecola C, DeAngelis LM, Kamel H, Okin PM, Gilchrist S, Soliman EZ, Cushman M, Muntner P. New diagnosis of cancer and the risk of subsequent cerebrovascular events. Neurology 2018; 90: e2025-e2033.

19) Woock M, Martinez-Majander N, Seiffge DJ, Selvik HA, Nordanstig A, Redfors P, Lindgren E, Sanchez van Kammen M, Rentzos A, Coutinho JM, Doyle K, Naess H, Putaala J, Jood K, Tatlisumak T. Cancer and stroke: commonly encountered by clinicians, but little evidence to guide clinical approach. Ther Adv Neurol Disord 2022; 15: 17562864221106362.

20) Thachil J, Falanga A, Levi M, Liebman H, Di Nisio M; Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH. J Thromb Haemost 2015; 13: 671-675.

21) Navi BB, Singer S, Merkler AE, Cheng NT, Stone JB, Kamel H, Iadecola C, Elkind MS, DeAngelis LM. Recurrent thromboembolic events after ischemic stroke in patients with cancer. Neurology 2014; 83: 26-33.

22) Navi BB, Marshall RS, Bobrow D, Singer S, Stone JB, DeSancho MT, DeAngelis LM. Enoxaparin vs Aspirin in Patients with Cancer and Ischemic Stroke: The TEACH Pilot Randomized Clinical Trial. JAMA Neurol 2018; 75: 379-381.

23) Martinez-Majander N, Ntaios G, Liu YY, Ylikotila P, Joensuu H, Saarinen J, Perera KS, Marti-Fabregas J, Chamorro A, Rudilosso S, Prats-Sanchez L, Berkowitz SD, Mundl H, Themeles E, Tiainen M, Demchuk A, Kasner SE, Hart RG, Tatlisumak T, NAVIGATE ESUS investigators. Rivaroxaban versus aspirin for secondary prevention of ischaemic stroke in patients with cancer: a subgroup analysis of the NAVIGATE ESUS randomized trial. Eur J Neurol 2020; 27: 841-848.

24) Tesfamariam B. Involvement of platelets in tumor cell metastasis. Pharmacol Ther 2016; 157: 112-119.

25) Zhang Q, Liu H, Zhu Q, Zhan P, Zhu S, Zhang J, Lv T, Song Y. Patterns and functional implications of platelets upon tumor "education". Int J Biochem Cell Biol 2017; 90: 68-80.
26) Karlińska AG, Gromadzka G, Karliński MA, Członkowska A. The activity of malignancy may determine stroke pattern in cancer patients. J Stroke Cerebrovasc Dis 2015; 24: 778-783.
27) Adams HP Jr. Cancer and Cerebrovascular Disease. Curr Neurol Neurosci Rep 2019; 19: 73.
28) Pan X, Zheng D, Zheng Y, Chan PWL, Lin Y, Zou J, Zhou J, Yang J. Safety and efficacy of tirofiban combined with endovascular treatment in acute ischaemic stroke. Eur J Neurol 2019; 26: 1105-1110.
29) Wu C, Sun C, Wang L, Lian Y, Xie N, Huang S, Zhao W, Ren M, Wu D, Ding J, Song H, Wang Y, Ma Q, Ji X. Low-Dose Tirofiban Treatment Improves Neurological Deterioration Outcome After Intravenous Thrombolysis. Stroke 2019; 50: 3481-3487.
30) RESCUE BT Trial Investigators, Qiu Z, Li F, Sang H, Luo W, Liu S, Liu W, Guo Z, Li H, Sun D, Huang W, Zhang M, Zhang M, Dai W, Zhou P, Deng W, Zhou Z, Huang X, Lei B, Li J, Yuan Z, Song B, Miao J, Liu S, Jin Z, Zeng G, Zeng H, Yuan J, Wen C, Yu Y, Yuan G, Wu J, Long C, Luo J, Tian Z, Zheng C, Hu Z, Wang S, Wang T, Qi L, Li R, Wan Y, Ke Y, Wu Y, Zhu X, Kong W, Huang J, Peng D, Chang M, Ge H, Shi Z, Yan Z, Du J, Jin Y, Ju D, Huang C, Hong Y, Liu T, Zhao W, Wang J, Zheng B, Wang L, Liu S, Luo X, Luo S, Xu X, Hu J, Pu J, Chen S, Sun Y, Jiang S, Wei L, Fu X, Bai Y, Yang S, Hu W, Zhang G, Pan C, Zhang S, Wang Y, Cao W, Yang S, Zhang J, Guo F, Wen H, Zhang J, Song J, Yue C, Li L, Wu D, Tian Y, Yang J, Lu M, Saver JL, Nogueira RG, Zi W, Yang Q. Effect of Intravenous Tirofiban vs Placebo Before Endovascular Thrombectomy on Functional Outcomes in Large Vessel Occlusion Stroke: The RESCUE BT Randomized Clinical Trial. JAMA 2022; 328: 543-553.
31) Seok JM, Kim SG, Kim JW, Chung CS, Kim GM, Lee KH, Bang OY. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol 2010; 68: 213-219.
32) van Dellen D, Tiivas CA, Jarvi K, Marshall C, Higman DJ, Imray CH. Transcranial Doppler ultrasonography-directed intravenous glycoprotein IIb/IIIa receptor antagonist therapy to control transient cerebral microemboli before and after carotid endarterectomy. Br J Surg 2008; 95: 709-713.
33) Saedon M, Singer DR, Pang R, Tiivas C, Hutchinson CE, Imray CH. Registry report on kinetics of rescue antiplatelet treatment to abolish cerebral microemboli after carotid endarterectomy. Stroke 2013; 44: 230-233.