Thrombolysis for Acute Ischemic Stroke in Taiwan

A-Ching Chao

Acta Neurol Taiwan 2010;19:225-227

Over the past 20 years, there have been several major advances in the care of patients with cerebrovascular diseases. The most important breakthrough is the use of intravenous thrombolysis for acute ischaemic stroke. Since the Department of Health of Taiwan approved the indication of tissue plasminogen activator (tPA) for acute ischemic stroke at the end of 2003, over 1,000 patients have been given intravenous thrombolytic therapy in Taiwan[1]. However, many important, unresolved problems still exist concerning tPA therapy in Taiwan, even in the whole world.

First, in America and Europe, the current tPA dose for acute ischemic stroke is 0.9 mg/kg. However, low-dose tPA (0.6 mg/kg) for acute ischemic stroke was approved in Japan in 2005[2]. Later many post-marketing studies in Japan also confirmed that low-dose therapy had similar outcomes compared with regular-dose therapy in Western patients[3,4]. Meanwhile, information on the benefit/risk profiles in the thrombolytic treatment of acute ischemic stroke in Chinese people was rare. In view of this, the Taiwan Stroke Society initiated a multicenter, observational study, the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study, and found the standard-dose group had significantly higher rates of symptomatic intracerebral hemorrhage (SICH) and mortality, twice that of those in the lower-dose group; and significantly lower independence rate compared with the lower-dose group; especially among patients ≥ 70 years old[5]. However, there was a different result reported by China[6], and even conflicting and inconclusive results from country to country in Asia. About dosage and ethnicity issues in tPA, we need randomized controlled clinical trials to settle the controversies.

Second, in light of the proportion of older patients is rapidly arising in our society, one would ask is thrombolysis safe in the elderly? In Europe, tPA is not recommended for stroke patients older than 80 for fear of excessive risk of SICH. Yet, studies from North America have revealed no association between age greater than 80 years old and risks of SICH. Taiwan followed the European license. Recently, there were two studies which stressed this topic and had different results again. One from Europe, it concluded odds for improved outcomes in patients with ischaemic stroke who receive thrombolysis were similar in those aged ≤ 80 and > 80, and age alone should not be a barrier to thrombolysis[7]. Another from US, it showed that the presence of intracerebral hemorrhage (ICH) was associated with higher mortality rates but not the use of thrombolysis among those > 80 years; however, the use of thrombolysis was associated with high risk of ICH[8]. So although thrombolysis in the elderly population is not prohibited in US, physicians must be careful for the

From the Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital and Kaohsiung Medical University Hospital and Department of Neurology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.
Received December 22, 2010. Accepted December 22 2010.

Correspondence to: A-Ching Chao, MD.
Department of Neurology, Kaohsiung Medical University Hospital No.100, Shih-Chuan 1st Road, Kaohsiung, Taiwan 807.
E-mail: achch@cc.kmu.edu.tw

potential complication of ICH. Still, inferences of these points should be cautious because these were not randomized studies. According to the TTT-AIS study[5], there are interactions between age and tPA dose, should we use a different dose of tPA for different age categories? More extensive data from randomized controlled trials would more conclusively answer this topic.

Third, not only in Taiwan but also in all other countries there are still a room for increasing the percentage of patients receiving tPA treatment. According to an analysis of the National Inpatient Sample database from US for the years 2000-2006, a very low rate of thrombolysis in the total cohort was found (1.51%)[8]. Various phases of barriers to thrombolysis have been identified, including prehospital delay and in-hospital delay. Aggressive, combined educational programs aimed at the general public, general practitioners, and medical and paramedical hospital staff can reduce prehospital delay[9]. Establishment of a primary stroke center (PSC) at a community hospital has been shown to be able to significantly decrease in-hospital delay[10]. The article published in this issue of Acta Neurologica Taiwanica by Sung SF et al showed the same results[11]. Following the establishment of the PSC, they achieved a 2.3-fold increase in the proportion of stroke patients treated with tPA. However, like other studies, there are also some areas of weakness. This study was observational, and selection bias was a possibility. Besides, the sample size was small.

Lastly, more and more studies provide compelling evidences that either a PSC or a comprehensive stroke center (CSC) saves lives and improves outcomes for patients with ischemic stroke[12]. Currently more and more stroke centers are organized in Taiwan. However, some questions will be faced immediately, such as what's the most suitable criteria of PSC or CSC in Taiwan? What organizations can fairly certify stroke centers? How many stroke centers do we need in view of the cost-effectiveness[13]? And do we have any program to preferentially transfer patients with acute stroke to the nearest PSC? We believe neurologists and health-care leaders in Taiwan will finally find their ways.

REFERENCES

1. Hsieh FI, Lien LM, Chen ST, Bai CH, Sun MC, Tseng HP, Chen YW, Chen CH, Jeng JS, Tsai SY, Lin HJ, Liu CH, Lo YK, Chen HJ, Chiu HC, Lai ML, Lin RT, Sun MH, Yip BS, Chiou HY, Hsu CY; Taiwan Stroke Registry Investigators. Get With the Guidelines-Stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry: Get With the Guidelines-Stroke in Taiwan. Circulation 2010;122:1116-1123.
2. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y; Japan Alteplase Clinical Trial (J-ACT) Group. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006;37:1810-1815.
3. Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T; Japan Alteplase Clinical Trial II Group. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). Stroke 2010;41:461-465.
4. Nakagawara J, Minematsu K, Okada Y, Tanahashi N, Nagahiro S, Mori E, ShinoharaY, Yamaguchi T; J-MARS Investigators. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). Stroke 2010;41:1984-1989.
5. Chao AC, Hsu HY, Chung CP, Liu CH, Chen CH, Teng MM, Peng GS, Sheng WY, Hu HH; the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) Study Group. Outcomes of Thrombolytic Therapy for Acute Ischemic Stroke in Chinese Patients. The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) Study. Stroke 2010;41:885-890.
6. Zhou XY, Wang SS, Collins ML, Davis SM, Yan B. Efficacy and safety of different doses of intravenous tissue plasminogen activator in Chinese patients with ischemic stroke. J Clin Neurosci 2010;17:988-992.
7. Mishra NK, Diener HC, Lyden PD, Bluhmki E, Lees KR; VISTA Collaborators. Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA). Stroke 2010;41:2840-2848.

8. Alshekhlee A, Mohammadi A, Mehta S, Edgell RC, Vora N, Feen E, Kale S, Shakir ZA, Cruz-Flores S. Is thrombolysis safe in the elderly?: analysis of a national database. Stroke 2010;41:2259-2264.
9. Bouckaert M, Lemmens R, Thijs V. Reducing prehospital delay in acute stroke. Nat Rev Neurol 2009;5:477-483.
10. Lattimore SU, Chalela J, Davis L, DeGraba T, Ezzeddine M, Haymore J, Nyquist P, Baird AE, Hallenbeck J, Warach S; NINDS Suburban Hospital Stroke Center. Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: the NINDS Suburban Hospital Stroke Center experience. Stroke 2003;34:e55-e57.
11. Sung SF, Ong CT, Wu CS, Hsu YC, Su YH. Increased use of thrombolysis therapy and shortening of in-hospital delays following acute ischemic stroke: experience on the establishment of a primary stroke center at a community hospital. Acta Neurol Taiwan 2010;19:260-264.
12. Meretoja A, Roine RO, Kaste M, Linna M, Roine S, Juntunen M, Erilö T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Effectiveness of primary and comprehensive stroke centers: PERFECT stroke: a nationwide observational study from Finland. Stroke 2010;41:1102-1107.
13. Demaerschalk BM, Hwang HM, Leung G. Cost analysis review of stroke centers, telestroke, and rt-PA. Am J Manag Care 2010;16:537-544.