Development of new revascularization therapy strategies for extending the time window and making a therapeutic breakthrough against acute ischemic stroke.

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The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study proved the efficacy and safety of intravenous (i.v.) recombinant tissue-type plasminogen activator (rt-PA) therapy by using alteplase at a dose of 0.9 mg/kg in 1995, when the diffusion-weighted image (DWI) also became available in a routine clinical use. The developments and clinical applications of these measures, rt-PA and DWI, have brought about a tremendous revolution in acute stroke management all over the world.

Since the late 1980's, the author has performed many clinical and experimental studies. He demonstrated that an early spontaneous recanalization of the occluded major cerebral arteries often causes a dramatic improvement and good clinical outcome in severe hemispheral ischemic stroke patients (Spectacular Shrinking Deficit)[1)]. He demonstrated firstly that the spreading depression phenomena occur in a primate stroke model[2)]. He reported many experimental DWI studies of reperfusion and neurovascular protection therapies in a rat stroke model[3-7)]. These results provided the theoretical grounds to the i.v. rt-PA therapy and DWI diagnosis in a clinical setting.

The author also contributed to accomplish the phase III clinical trial named Japan Alteplase Clinical Trial (J-ACT)[8)], which confirmed the efficacy and safety of i.v. rt-PA therapy at a dose of 0.6 mg/kg for Japanese patients, and brought about the approval of the therapy by the Japanese Government in 2005. After the approval, the author participated greatly in making the Japan Stroke Society Guideline of i.v. rt-PA therapy, and in planning and executing many clinical studies and registries in Japan, including Stroke Unit Multicenter Observational (SUMO) Study, the National Cerebral and Cardiovascular Center (NCVC) rt-PA Registry, the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Register, a clinical trial of J-ACT II, and the nation-wide post-marketing registry of J-MARS[9-15)]. These studies demonstrated consistently that the i.v. alteplase therapy at a dose of 0.6 mg/kg resulted in a relatively good outcome, being comparable to results of similar post-marketing studies using i.v. alteplase at a dose of 0.9 mg/kg in

the North-America and Europe. For these years, he has played a role of the principal investigator of many national research projects for a stroke unit, stroke indicators, the relation of antiplatelet therapy to intracranial hemorrhage, cervicocepahic arterial dissection and transient ischemic attacks (TIA)[16-22].

Numerous clinical studies have been performed all around the world to make the therapeutic time window extend form the initial 3 hours to the 4.5 hours with i.v. alteplase therapy, to the 9 hours with a new rt-PA, desmoteplase, and to the 8.5 hours with new intravascular devices such as the Merci and Penumbra. The author will try to set new therapeutic strategies, including the above-mentioned techniques, transcranial low-frequency sonothrombolysis and a combination therapy of i.v. rt-PA therapy with other measures, such as intraarterial thrombolysis, intravascular ultrasounds, and mechanical intravascular devices for extending the time window and making a new breakthrough against acute ischemic stroke.

References

1. Minematsu K, Yamaguchi T, Omae T: Spectacular shrinking deficit: Rapid recovery from a major hemispheric syndrome by migration of an embolus. Neurology, 42: 157-162, 1992.
2. Yokota C, Kuge Y, Hasegawa Y, … Minematsu K: Unique profile of spreading depression in a primate model. J Cereb Blood Flow Metab, 22: 835-842, 2002.
3. Minematsu K, Li L, Fisher M, Sotak CH, et al: Diffusion weighted magnetic resonance imaging: Rapid and quantitative detection of focal brain ischemia. Neurology, 42: 235-240, 1992
4. Fisher M, Sotak CH, Minematsu K, Li L: New magnetic resonance techniques for evaluating cerebrovascular disease. Ann Neurol, 32: 115-122, 1992
5. Minematsu K, Li L, Sotak CH, et al: Reversible focal ischemic injury demonstrated by diffusion-weighted magnetic resonance imaging in rats. Stroke, 23: 1304-1311, 1992
6. Minematsu K, Fisher M, Li L, et al: Effects of a novel NMDA antagonist on experimental stroke rapidly and quantitatively assessed by diffusion weighted MRI. Neurology, 43: 397-403, 1993
7. Minematsu K, Fisher M, Li L, Sotak CH: Diffusion and perfusion magnetic resonance imaging studies to evaluate a noncompetitive N-methyl-D-aspartate antagonist and reperfusion in experimental stroke in rats. Stroke, 24: 2074-2081, 1993

8. Yamaguchi T, Mori E, Minematsu K, et al.: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset. Japan Alteplase Clinical Trial (J-ACT). Stroke, 37:1810-1815, 2006.
9. Ogawa A, Mori E, Minematsu K, et al.: Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke. The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. Stroke, 38: 2633-2639, 2007.
10. Mori E, Minematsu K, Nakagawara J, et al. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcome in middle cerebral artery occlusion. Japan Alteplase Clinical Trial II (J-ACT II). Stroke, 41: 461-465, 2010.
11. Nakashima T, Toyoda K, Koga M, … Minematsu K: Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. Int J Stroke, 4:425-431, 2009.
12. Toyoda K, Koga M, Naganuma M, … Minematsu K, for the Stroke Acute Management with urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators: Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients. General outcome and prognostic factors from the SAMURAI Register. Stroke, 40:3591-3595, 2009.
13. Nezu T, Koga M, Kimura K, … Minematsu K, Toyoda K: Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA. SAMURAI rt-PA Registry. Neurology, 75:555-561, 2010.
14. Nakagawara J, Minematsu K, Okada Y, et al. 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, 41: 1984-1989, 2010.
15. Hirano T, Sasaki M, Mori E, Minematsu K, et al: Residual vessel length on magnetic resonance angiography identifies poor responders to alteplase in acute middle cerebral artery occlusion patients. Exploratory analysis of the Japan Alteplase Clinical Trial II. Stroke, 41:2828-2833, 2010.
16. Ogata J, Yutani C, Otsubo R, … Minematsu K: Heart and vessel pathology underlying brain infarction in 142 stroke patients. Ann Neurol, 63: 770-781, 2008.
17. Toyoda K, Yasaka M, Iwade K, … Minematsu K: Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective multicenter observational study. Stroke, 39: 1740-1745, 2008.
18. Toyoda K, Yasaka M, Uchiyama S, … Minematsu K, on behalf of The Bleeding With Antithrombotic Therapy (BAT) Study Group: Blood pressure levels and

bleeding events during antithrombotic therapy. The Bleeding with Antithrombotic Therapy (BAT) Study. Stroke, 41: 1440-1444, 2010.
19. Yoshimura S, Toyoda K, Ohara T, …, Minematsu K: Takotsubo cardiomyopathy in acute ischemic stroke. Ann Neurol, 64: 547-554, 2008.
20. Sato S, Uehara T, Toyoda K, …, Minematsu K, the Stroke Unit Multicenter Observational (SUMO) Study Group: Impact of the approval of intravenous recombinant tissue plasminogen activator therapy on the processes of acute stroke management in Japan: The Stroke Unit Multicenter Observational (SUMO) Study. Stroke, 40: 30-34, 2009.
21. Sato S, Toyoda K, Matsuoka H, … Minematsu K: Isolated anterior cerebral artery infarction: Dissection as an etiological mechanism. Cerebrovasc Dis, 29:170-177, 2010.
22. Nakajima M, Hirano T, Naritomi H, Minematsu K: Symptom progression or fluctuation in transient ischemic attack patients predicts subsequent stroke. Cerebrovasc Dis, 29:221-227, 2010.