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

Kazuo Minematsu, MD, PhD
Deputy Director General of the Hospital
National Cerebral and Cardiovascular Center

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 hemispherical 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, cervicocephalic arterial dissection and transient ischemic attacks (TIA)\textsuperscript{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
18. Toyoda K, Yasaka M, Uchiyama S, … Minematsu K, on behalf of The Bleeding With Antithrombotic Therapy (BAT) Study Group: Blood pressure levels and