

# Intravenous Thrombolysis with Neuroprotective Therapy by Edaravone for Ischemic Stroke Patients Older than 80 Years of Age

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**Background:** Alteplase, a recombinant tissue plasminogen activator (tPA), was approved for patients with acute ischemic stroke within 3 hours of stroke onset in Japan in October 2005 at a dose of 0.6 mg/kg. The aim of this study was to assess the safety and efficacy of alteplase in elderly patients in Japan. **Methods:** One hundred twenty-nine consecutive patients who were admitted to our 5 hospital groups and who received intravenous tPA within 3 hours of stroke onset between January 2010 and December 2011 were divided into 2 groups by age (<80 years of age [younger group] and ≥80 years of age [older group]) and by treatment with or without edaravone. Clinical backgrounds and outcomes were investigated. **Results:** The National Institutes of Health Stroke Scale score on admission was not different in both groups, but the National Institutes of Health Stroke Scale scores 7 days after stroke onset were significantly higher in the older group (score 8;  $P < .05$ ) than in the younger group (score 4), and the ratio of patients with a modified Rankin Scale score of 4 to 6 was significantly greater in the older group (41.7%;  $P < .05$ ) than in the younger group (22.2%). However, there was no difference in asymptomatic and symptomatic intracerebral hemorrhage rates between the younger and older groups (asymptomatic 20.2% *v* 18.8%; symptomatic 2.6% *v* 2.1%). Patients with edaravone showed a higher recanalization rate (61.9%;  $P < .01$ ) and a better modified Rankin Scale score at 3 months post-stroke ( $P < .01$ ) than the nonedaravone group. **Conclusions:** These data suggest that intravenous alteplase (0.6 mg/kg) within 3 hours of stroke onset was safe and effective, even for very old patients (≥80 years of age), but resulted in poor outcomes relating not to tPA but to aging. In addition, edaravone may be a good partner for combination therapy with tPA to enhance recanalization and reduce hemorrhagic transformation. **Key Words:** Acute ischemic stroke—edaravone—elderly—intracerebral hemorrhage—recanalization—tissue plasminogen activator.

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Stroke is a leading cause of death and severe disability both in the developing and developed countries. Many approaches can be applied for primary and secondary preventions of stroke, including antihypertensive, antihyperlipidemic, antidiabetic, and antithrombotic therapies, but challenges still remain for acute stroke therapy to improve both symptoms and outcomes. Because ischemic brain damage depends on both duration after stroke onset and severity of the ischemia, both early recanalization and neurovascular protection are of extreme importance to obtain better outcomes for patients with acute stroke.

Alteplase, a recombinant tissue plasminogen activator (tPA), was approved for patients with acute ischemic stroke (AIS) in Japan in October 2005 at a dose of 0.6 mg/kg.<sup>1</sup> A free radical scavenger, edaravone, is an effective neurovascular protective treatment in cerebral infarction approved in 2001 only in Japan. Most AIS patients therefore take edaravone in combination with tPA treatment in Japan. Because intracerebral hemorrhage (ICH) is frequently a major complication in thrombolytic therapy with tPA,<sup>1</sup> an indication of tPA requires a careful evaluation of both the risks and the potential benefits.

Developed countries are rapidly aging, and stroke in the elderly is of their serious concern not only because of the higher incidence but also of the increasing disability after stroke. Many randomized controlled trials of thrombolysis in AIS exclude patients >80 years of age, but this demographic represents approximately one-third of patients with stroke in prospective registries.<sup>2</sup> As a result, there remains uncertainty about the risk to benefit profile of tPA in elderly patients.

With increasing experience with tPA during the last 7 years in Japan, several clinical parameters may have changed over time, such as prognosis, the frequency of hemorrhagic complications, and so on. Therefore, we retrospectively analyzed such clinical parameters and compared them in younger (<80 years of age) and older (≥80 years of age) patients in our 5 hospital groups. We report the current risk to benefit profile of intravenous tPA thrombolytic therapy for AIS.

## Methods

### *Patients*

This study retrospectively evaluated 129 consecutive patients (67 men and 62 women) between 34 and 101 years of age (mean ± SD 73.3 ± 13.9 years) with acute cerebral infarction who were admitted to our hospital groups (Okayama University Hospital, Okayama National Hospital Medical Center, Kurashiki Heisei Hospital, Okayama Kyokuto Hospital, and Okayama Citizens' Hospital). These patients received intravenous tPA within 3 hours of stroke onset between January 2010 and December 2011 (a 2-year period).

Risk factors for AIS, including hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), coronary ar-

tery disease (CAD), a history of smoking for >2 months, and previous stroke were evaluated. Other clinical backgrounds and outcomes were also investigated, including the use of oral antithrombotic drugs at stroke onset because of AIS, systolic blood pressure (SBP) and diastolic blood pressure before treatment, time to arrival at the hospital and the start of treatment, and the use of edaravone.

### *Clinical Diagnosis and Evaluations*

On admission, all patients were evaluated by neurologists with the National Institutes of Health Stroke Scale (NIHSS). Diffusion-weighted imaging (DWI) and T<sub>2</sub>-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) was performed to identify fresh infarction, and magnetic resonance angiography (MRA) was added for the evaluation of occlusive site of the cerebral arteries. Laboratory blood examinations, 12-lead electrocardiograms, and plain chest roentgenograms were performed in all patients. All patients were evaluated with the NIHSS on admission and 7 days after the onset and with the modified Rankin Scale (mRS) 3 months after stroke onset. Infarct size was evaluated with the DWI-Alberta Stroke Program Early CT Score (DWI-ASPECTS).<sup>3,4</sup> Recanalization was determined by MRA 24 to 72 hours posttreatment. Symptomatic ICH (sICH) was defined using a criteria the same as the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST; a ≥4-point increase in NIHSS score from baseline or death within 36 hours and local or remote parenchymal hemorrhage type 2 with a dense hematoma >30% of the lesion volume with significant space-occupying effect).<sup>5</sup> Patients were divided into 2 groups—those ≥80 years of age and those <80 years of age—because patients ≥80 years of age may have an increased risk of ICH, especially in developed countries.

### *Statistical Analysis*

For statistical analysis, the Mann-Whitney *U* or Chi-square test was used. A multiple logistic regression analysis was used for comparison of characteristics between the case group with and without recanalization. *P* < .05 was considered statistically significant. This study was approved by the ethics committee of each of the 5 hospitals.

## Results

The patients' baseline clinical characteristics, risk factors for stroke, type of cerebral infarction, and responsible occluded artery are shown in Table 1. Among the 129 patients who received intravenous tPA, 79 cases (61.2%) were cardiogenic embolism, 44 (34.1%) atherothrombosis, and 4 (3.1%) lacunar infarction. The responsible occluded

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