Thrombolysis with Low dose Tissue Plasminogen Activator 3–4.5 Hours After Acute Ischemic Stroke in 5 Hospital Groups in Japan

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Abbreviations: DWI, diffusion-weighted imaging; DWI-ASPECTS, diffusion weighted imaging –Alberta Stroke Program Early Computed Tomography Score; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; tPA, Tissue Plasminogen Activator;

Abstract

Background and Purpose: Clinical data from Japan on the safety and real-world outcomes of alteplase (tPA) thrombolysis in the extended therapeutic window are lacking. The aim of this study was to assess the safety and real-world outcomes of tPA administered within 3–4.5 hours of stroke onset.

Methods: The study comprised consecutive acute ischemic stroke patients (n = 177) admitted across 5 hospitals between September 2012 and August 2014. Patients received intravenous tPA within < 3 or 3–4.5 hours of stroke onset. Endovascular therapy was used for tPA refractory patients.

Results: In the 3–4.5 hour subgroup (31.6% patients), tPA was started 85 minutes later than the < 3 hour group (220 min vs. 135 min, respectively). However, outcome measures were not significantly different between the < 3 and 3–4.5 hour subgroups for recanalization rate (67.8 vs. 57.1%), symptomatic intracerebral hemorrhage (2.5 vs. 3.6%), modified Rankin Scale score of 0–1 at 3 months (36.0 vs. 23.4%) and mortality (6.9 vs. 8.3%). We present data from 2005–2012 using a therapeutic window < 3 hour showing comparable results. tPA following endovascular therapy with recanalization might be superior to tPA only with recanalization (81.0 vs. 59.1%).

Conclusions: Compared with administration within 3 hours of ischemic stroke onset, tPA is as safe and the same outcomes within 3–4.5 hours in real-world stroke emergency settings at multiple sites in Japan.

Key Words: Acute stroke; edaravone; endovascular treatment; intracerebral hemorrhage; recanalization; tissue-type plasminogen activator.

Introduction

Alteplase is a recombinant tissue plasminogen activator (tPA) approved in Japan for thrombolysis of ischemic stroke patients [1]. While previously approved for administration within 3 hours of stroke onset, the safety of tPA within 3–4.5 hours of onset was demonstrated by Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) [2]. The European Cooperative Acute Stroke Study III (ECASS III) [3] and other studies [4,5] demonstrated benefit of tPA in the extended time window.

Treatment guidelines were subsequently updated to recommend tPA treatment within 4.5 hours of stroke onset in Europe, the United States, Canada (in 2009) and in Australia (in 2010) [6-9]. Guidelines for Japan were updated accordingly in September 2012 by the Japan Stroke Society [10].

Edaravone is a free radical scavenger used for neurovascular protection in cerebral infarction and was approved for adjunct therapy in Japan in 2001 [11-14]. In addition to Japan, most acute ischemic stroke patients in China [15] and India [16] now receive edaravone in combination with tPA treatment.

Over the course of time since the tPA therapeutic window was extended in Japan, trends of other stroke protocol parameters may have changed, such as the time to treatment, prognosis and the frequency of hemorrhagic complications. Therefore, we retrospectively analyzed these clinical parameters within the context of comparing patients treated with alteplase within 3 hours or within 3–4.5 hours of stroke onset.

Materials and Methods

Patients

The study was approved by the ethics committee of Okayama University (#1505-025). Three groups of patients were established. The first included those patients receiving tPA within 3 hours of stroke onset during October 2005 to August 2012 (Period 1). The results of this observational study have been reported previously [17,18]. The second group included those patients receiving tPA within 3 hours of stroke onset from September 2012 to August 2014 (Period 2a) (after the therapeutic window extension). The third group comprised patients receiving tPA 3–4.5 hours after stroke onset from September 2012 to August 2014 (Period 2b).

For all patients in Period 2, we retrospectively evaluated 177 consecutive acute ischemic stroke patients (101 men) aged 39–95 years who were admitted to one of 5 hospitals between September 2012 and August 2014. The hospitals included Okayama University Hospital, Okayama National Hospital Medical Center, Kurashiki Heisei Hospital, Okayama Kyokuto Hospital and Okayama Citizens' Hospital. All Period 2 patients received intravenous tPA within 4.5 hours of symptom onset.

Risk factors for acute ischemic stroke were noted: hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, coronary artery disease, a history of smoking > 2 months, and previous stroke. Other factors included the use of antithrombotic drugs at stroke onset, systolic blood pressure and diastolic blood pressure before treatment, body mass index, latency to treatment, the use of edaravone, endovascular treatment, and laboratory data (blood glucose, hemoglobin A1c, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, blood urea nitrogen, creatinine and prothrombin time).

We compared time from admission to tPA treatment (door to needle) between patients treated in Periods 1 and 2. Similar to the previous report [19], we also calculated door-to-needle time based on symptom onset-to-admission time (onset to

door). For this purpose, we segmented onset-to-door time into 30-minute intervals and subsequently evaluated the median door-to-needle time per 30-minute interval.

Treatments

Patients in Period 2 were divided into the two subgroups for comparison: those treated within 3 hours and those treated within 3–4.5 hours. All Period 2 patients received tPA at a dose of 0.6 mg/kg, with 10% as a bolus and the remainder infused over one hour [10]. Edaravone was administered by intravenous route over 30 min twice a day. Administration of edaravone was initiated within 24 hours after the onset, and the duration of administration was within 14 days. The development of acute renal failure is reported as one of edaravone's serious adverse reactions, so patients with significant renal disorder were considered ineligible for edaravone [20]. If the patients had an occlusion of the internal carotid artery, or of the first or second segments of the middle cerebral artery, or of the basilar artery on magnetic resonance angiography (MRA) and were refractory to thrombolysis, they immediately underwent percutaneous transluminal angioplasty or thrombectomy with the Merci retriever, Penumbra System, Solitaire FR revascularization device or a standard microcatheter. For study inclusion, endovascular therapy had to begin within 8 hours of stroke onset.

Clinical Diagnosis and Evaluations

Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) and T_2-weighted or fluid-attenuated inversion recovery was performed to identify new infarction, and MRA was added for the evaluation of cerebral artery occlusions. Laboratory blood examinations, 12-lead electrocardiograms and plain chest X-rays

were performed in all patients. All patients were evaluated by neurologists using the National Institutes of Health Stroke Scale (NIHSS) on admission and at 7 days after the stroke onset, and with the modified Rankin Scale (mRS) at 3 months after stroke onset.

Infarct size was evaluated by using the DWI–Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) [21,22]. Recanalization was judged to have occurred with a modified Arterial Occlusive Lesion (mAOL) score of 2 or 3 using MRA 24–72 hours post-treatment [23].

Intracerebral hemorrhage (ICH) was defined using criteria from 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 [24].

Statistical Analysis

The chi-squared test was used for categorical variables and the Student's *t* test or the Mann-Whitney U test for continuous variables. $P < 0.05$ was considered statistically significant. To correct for multiple comparisons, we used Bonferroni correction.

Results

The number of patients treated with tPA increased year by year from October 2005 to August 2014 (Periods 1 and 2). In the last 3 years of Period 1, the average number of patients treated with tPA was 62.3/year. After September 2012, when the therapeutic window was extended until 4.5 hours of onset, the average number of

patients treated within 3 hours was 60.5/year (Period 2a) and those treated within 3–4.5 hours was 28.0/year (Period 2b). Thus, the number of patients treated with tPA in Period 2 increased 1.42-fold compared with those treated in the last 3 years of Period 1 (Fig. 1).

Baseline demographics, clinical characteristics and clinical outcomes of the 177 patients between September 2012 and August 2014 (Period 2) are summarized in Table 1. Among the 177 patients, 121 patients (68.4%) were treated within 3 hours (Period 2a) and 56 patients (31.6%) within 3–4.5 hours (Period 2b). Baseline demographic and clinical characteristics of Periods 2a/2b were similar (Table 1).

In patients treated within 3 and 3–4.5 hours, the median time from stroke onset to admission was 61 and 131 minutes, respectively ($P < 0.01$). The median time from door to needle in patients treated within 3 and 3–4.5 hours was 65 and 78 minutes, respectively ($P < 0.01$). Thus, the median time from stroke onset to needle in patients treated within 3 and 3–4.5 hours was 135 and 220 minutes, respectively ($P < 0.01$).

The median door-to-needle time was 70 minutes in Period 1 (< 3 hours) and 69 minutes in Period 2 (< 3 and 3–4.5 h; $P = 0.64$). As for the 30-minute interval comparison, the door-to-needle time showed similar times in Periods 1 and 2 at ≤ 30-minute, 31–60-minute and 61–90-minute onset-to-door times (Fig. 2). In contrast, the median door-to-needle time in Period 2 was longer than Period 1 for patients admitted at 91–120-minute ($P < 0.01$) and 121-180-minute onset-to-door times ($P < 0.05$) (Fig. 2, right).

Between patients treated within 3 and 3–4.5 hours there was no significant difference in NIHSS score, mRS score, the proportions of asymptomatic and symptomatic ICH, and mortality. Recanalization rate tended to be higher in patients treated within 3 hours than 3–4.5 hours (65.0% vs. 57.1%; $P = 0.17$).

Endovascular therapy was performed in 22 of the 177 patients (12.4%) (Table 1), with thrombectomy in 63.6% of cases, percutaneous transluminal angioplasty in 27.3% of cases and 9.1% with other devices. Recanalization was obtained in 21/22 patients (95.5%). All Period 2 patients were divided into the three subgroups depending on the nature of recanalization and endovascular therapy (Table 2): tPA alone without recanalization (n = 62, 35.0%), tPA alone with recanalization (n = 93, 52.5%), and tPA with recanalization following endovascular therapy (n = 21, 11.9%). Compared with the group of tPA without recanalization, the group of tPA with recanalization showed lower median NIHSS scores at 7 days after onset (6 vs. 2; $P < 0.01$) and higher rate of mRS score 0-1 at 3 months (9.8% vs. 44.4%, $P < 0.01$). Compared with the group of tPA alone with recanalization, the group of tPA following endovascular therapy with recanalization might suggest a lower median DWI-ASPECTS (9 vs. 7; $P < 0.05$) and higher median NIHSS scores on admission (10 vs. 21; $P < 0.01$) and at 7 days after onset (2 vs. 4; $P < 0.05$). There was no significant difference in mRS score, mortality and ICH at 3 months (Table 2). We next analyzed the proportion of favorable clinical responses in these three subgroups, defined as a NIHSS score reduction ≥ 8 points or reaching 0–1 at 7 days (Fig. 3). Compared with tPA alone without recanalization, the groups of tPA with recanalization, and tPA with recanalization following endovascular therapy might suggest a higher rate of favorable clinical responses (11.3% vs. 59.1% vs. 81.0%, respectively) despite baseline NIHSS favoring the non-endovascular group.

Among 177 patients, 163 patients (92.1%) received the free radical scavenger edaravone; 14 patients (7.9%) did not receive edaravone due to significant renal disorder. The edaravone group might suggest more frequent recanalization (66.3% vs. 35.7%) and a lower rate of symptomatic ICH (1.8% vs. 21.4%) than the non-

edaravone group (Table 3). Of 56 patients receiving tPA within 3–4.5 hours (Period 2b), 51 patients (91.1%) were in the edaravone group. 5 patients (8.9%) were in the non-edaravone group because of significant renal disorder. Patients in the edaravone group might suggest more frequent recanalization than the non-edaravone group (62.7% vs. 0%) (Table 4).

Discussion

The number of patients receiving tPA has increased every year across our group of hospitals. A 42% increase in tPA treatments was observed in the period from 2012–2014 compared with 2009–2012, which is comparable to that reported by Cronin et al [25]. Furthermore, the ratio of 3–4.5 h/<3 hour tPA treatments was 31.6%, which was higher than previous reports by Cronin et al. (15.3%) [25] and Ahmed et al. (19.7%) [19]. In the present study, compared with patients administered tPA within 3 hours of onset, patients treated within 3–4.5 hours showed similar outcomes for symptomatic ICH, functional independence (mRS score 0–1) and mortality at 3 months, which was consistent with other studies [2,25]. However, the outcomes of the group treated within 3–4.5 hours were worse than those of previous studies. The frequency of symptomatic ICH (3.6%) was higher than ECASS III (1.9%) and SITS-ISTR (2.2%), but lower than other previous reports (4.3–5.1%) [2-4,25], and the rate of functional independence (mRS score 0–1) at 3 months (23.4%) was lower than previous reports (37.0–52.4%) [2-4]. These differences could be partly due to baseline differences, in which the present study included 27 patients (48.2%) who didn't meet ECASS III criteria such as over 80 years old (n=21, 37.5%), a higher NIHSS score 25 on admission (n=2, 3.6%), anticoagulant use (n=6, 10.7%), systolic pressure greater than 185 mmHg or diastolic pressure greater than 110mmHg (n=1, 1.8%) and

combination of previous stroke and diabetes mellitus (n=1, 1.8%). Compared with the patients who met ECASS III criteria (n=29, 51.7%), these 27 patients who didn't meet ECASS III criteria were older (83.3 vs 68.5) and showed higher median NIHSS scores on admission (18 vs. 9), and lower rate of mRS score 0-1 at 3 months (10.0% vs. 33.3%). There was no significant difference in ICH at 3 months between these groups. With regard to our patients who met ECASS III criteria (n=29), median NIHSS on admission was as high as ECASS III and SITS-ISTR (9 vs 9 vs 11, respectively). However the rate of mRS score 0–1 at 3 months (n=9, 34.6%) was lower than ECASS III (52.4%) and SITS-ISTR (40.5%), the frequency of symptomatic ICH (n=1, 3.4%) was higher than ECASS III (1.9%) and SITS-ISTR (2.2%), and mortality at 3 months (n=2, 6.9%) was lower than ECASS III (7.7%) and SITS-ISTR (7.5%) [2,3]. Our sample size is too small, so further accumulation of data is needed.

The median door-to-needle time was similar between the tested periods until 90 minutes of onset-to-door time. Door-to-needle time was longer in Period 2 than Period 1 after 90 minutes of onset-to-door time, which maybe partly due to confounding by the extended therapeutic window patients. More patients are being treated in period 2, but in some cases this would be taking longer. This might reflect the human tendency to be driven by a deadline, or it might reflect that some patients who otherwise might not have gotten treated at all are now being treated because of the extended time window. Longer onset-to-door time was associated with a shorter door-to-needle time, including the extended therapeutic window patients. These results were similar to those of the previous study [19]. Although it is limited to compare the outcomes because of the baseline differences among subgroups, the present study might suggest that recanalization after tPA would give a better outcome

and lower mortality. Endovascular therapy after tPA also might suggest the possibility of a better outcome than tPA alone. This result was similar to the previous reports [26-29].

Edaravone is a free radical scavenger and neuroprotectant, which was approved in Japan in 2001 as an adjunct treatment of ischemic stroke within 24 hours of symptom onset [11-14]. In the present study, the edaravone group, even within 3–4.5 hours following symptom onset, might suggest higher rates of recanalization than the non-edaravone group. Similar results have been reported by ourselves and others within 3 hours [17,18,30]. It has been extensively reported in vitro and in vivo that edaravone inhibits brain edema [11], ischemic brain injury with protection of neurovascular unit [31-34], and vascular endothelial cell injury after ischemia [35]. Edaravone might complements tPA therapy up to 4.5 hours of stroke onset by protecting neurovascular unit. Further study will be required in the form of a randomized controlled trial where edaravone is not the standard of care.

The present study has several limitations. This is a retrospective cohort study and therefore treatments chosen for each patient depends on that patient's characteristics and baseline. Endovascular therapy was limited to the patients who were refractory to thrombolysis with large vessel occlusion. Edaravone wasn't administered for patients with significant renal disorder because it may cause fatal acute renal failure. There are these baseline differences between subgroups and confounding by indication, so we cannot legitimately compare the therapeutic outcomes of endovascular therapy and edaravone. The differences between subgroups cannot be attributed to the treatment itself in the absence of a well-done RCT with balanced arms. Future studies with greater number of cases randomly assigned and matched with baseline will be needed.

In conclusion, the present study showed that intravenous alteplase administered within 3–4.5 hours of stroke onset was safe in the real-world stroke emergency setting, and that the clinical outcomes and incidence of ICH are comparable with previous data for treatment within 3 hours of stroke onset.

Compliance with Ethical Standards

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Conflict of Interest: Edaravone has been marketed in Japan since 2001 by Mitsubishi Tanabe Pharma (Osaka, Japan). K. Abe received honoraria from Mitsubishi Tanabe Pharma (Osaka, Japan) in 2012, 2013 and 2014. All remaining authors report no conflicts of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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Figure Legends

Figure 1. Number of patients treated with tPA per year from 2005 to 2014. Period 1 October 2005–September 2012 (tPA ≤ 3 hours) and Period 2, September 2012–2014 (≤ 4.5 hours). Period 2 is further divided into subgroups tPA within 3 hours (Period 2a) and 3–4.5 hours (Period 2b).

Figure 2. Relationships between onset-to-door time and door-to-needle time in Periods 1 and 2. Longer onset-to-door time was associated with shorter door-to-needle time, including Period 2b patients. The door-to-needle time was similar in Periods 1 and 2 until 90 minutes of onset-to-door time, but became longer in Period 2 than Period 1 after 90 minutes of onset-to-door time (*$P < 0.05$, ** $P < 0.01$).

Figure 3. Proportions of favorable clinical responses following recanalization and endovascular treatment, defined as NIHSS reduction ≥ 8 points or reaching 0–1 at 7 days. Recanalization after tPA only (59.1%) was improved following endovascular treatment (81.0%).