Simultaneous Administration of Recombinant Tissue Plasminogen Activator and Edaravone in Acute Cerebral Ischemic Stroke Patients

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Among the 1052 patients admitted to our hospital because of cerebral infarction between January 1, 2007, and December 31, 2010, we report the treatment outcomes of 48 patients (4.6% of all patients) who received recombinant tissue plasminogen activator (rt-PA) therapy (simultaneously combined with edaravone) within 3 hours after the onset of infarction. Twenty (41.7%) patients started receiving edaravone before rt-PA administration, and 28 patients (58.3%) started receiving rt-PA and edaravone simultaneously. The patients had an average age of 73.5 years (range, 55-93 years; male:female, 32:16). Medical histories included hypertension, diabetes mellitus, dyslipidemia, arterial fibrillation, and a smoking history in 23 (47.8%), 7 (14.6%), 8 (16.7%), 29 (60.4%), and 8 (16.7%) of patients, respectively. Regarding the treatment outcome of the therapy, the National Institutes of Health Stroke Scale score, which was 15 points before rt-PA administration, showed a statistically significant improvement to 8 points after rt-PA administration ($P < .001$). The modified Rankin Scale scores at 90 days after treatment were as follows: 0 in 12 patients (25.0%), 1 in 11 patients (22.9%), 2 in 7 patients (14.6%), 3 in 5 patients (10.4%), 4 in 6 patients (12.5%), 5 in 5 patients (10.4%), and 6 in 2 patients (4.2%). The occluded blood vessel reopened completely in 30 patients (62.5%) and partially in 5 patients (10.4%). Asymptomatic hemorrhage over the entire brain developed in 2 patients (4.2%). Thus, rt-PA therapy in combination with edaravone improved the recanalization rate, reduced the incidence of intracranial hemorrhage, and improved functional prognosis. **Key Words:** Edaravone—recombinant tissue plasminogen activator—cerebral infarction—rehabilitation.

Introduction

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) has been well established as a standard therapy for the treatment of acute phase cerebral infarction since its approval in 2005 in Japan.[1,2] However, to the present date, the associated complications, including hemorrhagic transformation and worsening of brain edema after rt-PA administration, have not been resolved.[3,4] Thus, it is important to overcome these challenges to improve the outcome of this therapy.

Edaravone is a therapeutic drug that has been used in everyday clinical practice to reduce brain damage[5] and improve functional prognosis[6] after acute phase cerebral infarction. Its major pharmacologic action involves

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scavenging of free radicals that develop after cerebral infarction. We hypothesized that administration of edaravone before rt-PA can inhibit vascular endothelial cell injury and neuronal cell damage that occurs after rt-PA administration, resulting in the improvement of the treatment outcome. Since 2007, we attempted to administer edaravone in a timely manner before (or at the same time of) rt-PA administration within 3 hours after the onset of cerebral infarction in patients who had been receiving rt-PA. This attempt was also conducted as part of a case series study.

Our results showed that an improvement in the functional prognosis at 90 days after treatment was achieved. Thus, we report these findings and provide bibliographical citations.

Subjects and Methods

Among the 1052 patients with cerebral infarction who were urgently transferred to the emergency outpatient unit of our hospital over the 4 years between January 1, 2007, and December 31, 2010, we studied 48 patients (4.6% patients) for whom the time of onset cerebral infarction was identified and who received intravenous rt-PA and edaravone (Radicut Injection; Mitsubishi Tanabe Pharma Corp, Osaka, Japan) treatments within 3 hours after the onset of symptoms. The average age of the 48 patients was 73.5 years (range, 55-93 years; male:female, 32:16). Medical histories included hypertension in 23 patients (47.8%), diabetes mellitus in 7 patients (14.6%), dyslipidemia in 8 patients (16.7%), arterial fibrillation in 29 patients (60.4%), and a smoking history in 8 patients (16.7%). After the patients were urgently transferred, they were treated according to the Japanese Guidelines for the Management of Stroke.

All patients who were transferred to our hospital underwent blood sampling, infusion for fluid replacement (extracellular fluid solution) in the emergency department, and a computed tomography (CT) scan in a timely manner. After evaluation of the neurologic findings, an examination of paralysis in the 4 extremities, an assessment using the National Institutes of Health Stroke Scale (NIHSS), and confirmation of an absence of renal dysfunction based on blood test results, the patients received an intravenous bolus infusion of edaravone over approximately 30 minutes before rt-PA administration. During this procedure, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) tests were added if time had permitted. After checking the vital signs and reassessing the NIHSS score, to confirm the stability of the patient's general condition, rt-PA was administered and the patient was moved to an intensive care unit (ICU). In the ICU, the patient continued to be treated according to the vital signs and the NIHSS score. Within 1-3 days after the start of the treatment, the patient again underwent CT, MRI, and MRA tests to confirm the presence/absence of hemorrhage, recanalization status of the occluded blood vessel, and severity of brain edema. Patients without recanalization were not excluded from the study. The subtypes of ischemic stroke were classified by the Trial of Org 10172 in Acute Stroke Treatment system.[7] The outcomes at 90 days after treatment were scored using the modified Rankin Scale (mRS).

This attempt to coadminister rt-PA and edaravone to these patients was approved by the Ethics Committee of Takayama Red Cross Hospital. The NIHSS score data were compared between the 2 stages (pre or postadministration). The significance of interstage differences was assessed using a t test. Values of P less than .05 were considered significant.

Results

With respect to the timing of edaravone administration in the 48 patients who received rt-PA (combined with edaravone), 20 patients (41.7%) started to receive edaravone before rt-PA administration and 28 patients (58.3%) started to receive rt-PA and edaravone simultaneously. The mean time from the onset of symptoms to intravenous edaravone infusion was 96 minutes (range, 60-170 minutes), and the mean time from the onset of symptoms to intravenous rt-PA administration was 127 minutes (range, 73-178 minutes).

Areas of cerebral infarction included the anterior cerebral artery in 2 patients (left side [L]:right side [R], 2:0; 4.2%), internal carotid artery in 9 patients (L:R, 4:5; 18.8%), middle cerebral artery in 35 patients (L:R, 20:15; 72.9%), and basilar artery in 2 patients (4.2%). The types of cerebral infarction included small artery occlusion (lacune) in 6 patients (12.5%), large artery atherosclerosis in 15 patients (31.2%), and cardioembolism in 27 patients (56.2%). Although the NIHSS score before rt-PA administration was 15 $\pm$ 6.4 points, the NIHSS score after rt-PA administration improved to 8 $\pm$ 8.5 points (statistically significant difference, $P < .001$; Fig 1). With respect to the recanalization rate, complete recanalization was observed in 30 patients (62.5%) and partial recanalization was observed in 5 patients (10.4%). The outcomes at 90 days after treatment, as assessed using mRS scores, were as follows: 0 in 12 patients (25.0%), 1 in 11 patients (22.9%), 2 in 7 patients (14.6%), 3 in 5 patients (10.4%), 4 in 6 patients (12.5%), 5 in 5 patients (10.4%), and 6 in 2 patients (4.2%; Fig 2).

Seven patients (14.6%) received an additional endovascular therapy because their symptoms did not improve by rt-PA administration, and their occluded blood vessel did not reopen. These 7 patients were classified as severe cases because of strong disturbance of consciousness at admission and an average NIHSS score of 20 points before drug treatment. Nevertheless, aggressive intervention using endovascular therapy induced recanalization in 2 patients. The mRS scores of the 7 patients at