Outcome of Acute Ischemic Stroke after the Treatment with Edaravone and 0.6 Mg/Kg Alteplase in Japanese Patients with Diabetes

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Background: We investigated how diabetes mellitus (DM) affects the outcome of acute ischemic stroke (AIS), comparing with the outcomes in those who had hypertension (HT) and atrial fibrillation (AF). *Methods:* This study was a subanalysis of PROTECT4.5, which was previously performed as a large-scale, prospective observational study of edaravone with approximately 10,000 patients with AIS in Japan. The study patients treated with edaravone alone or edaravone + alteplase (recombinant tissue plasminogen activator [tPA]) were analyzed for their outcomes and explored for the risk factors of poor outcome, after being divided into 8 groups according to their affected complications of DM, HT, or AF in the groups treated with edaravone alone or edaravone + tPA. *Results:* Among patients treated with edaravone alone and edaravone + tPA, the mean reduction in the National Institutes of Health Stroke Scale from baseline to 3 months after the onset was 2.0 and 4.4 in DM groups, respectively. The reduction was smaller in these groups compared with other groups (3.3-4.3 and 6.0-7.7, respectively). The logistic regression model revealed that DM was an independent risk factor for highly unfavorable outcome of modified Rankin Scale score 3-6 at 3 months after the onset, among both patients treated with edaravone alone and those treated with edaravone + tPA (odds ratio [OR]: 2.23, 95% confidential interval [CI]: 1.42-3.50 and OR: 2.05, 95% CI: 1.33-3.14, respectively). *Conclusions:* DM is suggested to adversely affect the outcome of AIS in Japanese patients. **Key Words:** Acute ischemic stroke—outcome—diabetes mellitus—clinical practice—Japan.

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Introduction

Diabetes mellitus (DM),[1-4] hypertension (HT),[5,6] and atrial fibrillation (AF)[7,8] are already known risk factors of stroke. These disorders are also associated with poor outcomes of acute ischemic stroke (AIS). Kamouchi et al analyzed the data of 3267 Japanese patients with acute stroke, and indicated that HbA1c on admission was an independent, significant predictor for neurologic and functional outcomes in patients with ischemic stroke.[9] A systematic review of 54 previous reports also concluded that history of DM and admission glucose levels are associated with poor clinical outcome after thrombolysis in patients with AIS.[10] Furthermore, high blood pressure has been reported to be an independent prognostic factor for poor outcome in the analysis of 17,398 patients with ischemic stroke.[11] Compared with patients without AF, patients with AF are reported to have a longer total length of hospital stay (median: 9 versus 15 days), and are at an increased risk of in-hospital medical complications (adjusted relative risk = 1.48, 95% confidential interval [CI]: 1.23-1.79).[12]

Currently, only a few reports have investigated how DM affects the outcome of AIS, comparing with the outcomes in patients with AIS who have HT and AF. A large-scale prospective observational study of edaravone with approximately 10,000 patients with AIS was recently performed in Japan (Post-marketing Registry On Treatment with Edaravone in acute Cerebral infarction by the Time window of 4.5 hours [PROTECT4.5]).[13] In the current study, sub-analyses of PROTECT4.5 were additionally performed to investigate the influences of DM, HT, and AF on the outcome of patients with AIS after the treatment with edaravone alone or edaravone + recombinant tissue plasminogen activator (tPA).

Methods

Study Design

This was a sub-analysis of PROTECT4.5,[13] previously performed as a prospective cohort study of edaravone in Japanese clinical practice from April 2010 to March 2013. In PROTECT4.5, study patients were treated with edaravone alone or edaravone + tPA. The number of registered patients was 11,384, and 1121 medical centers across Japan participated in the PROTECT4.5. The trial is registered under the number UMIN000009227. The primary purpose of current sub-analysis of PROTECT4.5 was to investigate how DM affects the outcome of AIS, comparing with the outcomes in patients with AIS who had HT and AF.

Subjects

Among study populations of previous PROTECT4.5, subjects of the present sub-analysis were defined as the patients who could be medically checked and recorded for their complications of DM, HT or AF by the physicians at each site. The inclusion criteria of PROTECT4.5 were as follows: patients with AIS receiving edaravone within 4.5 hours of onset, a consciousness level of 0-30 by the Japan Coma Scale,[14] and weakness in the upper or lower limbs (hemiparesis or hemiplegia). The exclusion criteria were baseline serum creatinine level more than 1.5 mg/dL, history of hypersensitivity to components of edaravone, ineligibility to participate in the study as judged by the attending physician because of the presence of severe liver disease (e.g., hepatic cirrhosis) or heart disease (e.g., congestive heart failure) requiring hospitalization, infection-related complications requiring administration of antibiotics, or other reasons; modified Rankin Scale score (mRS) equal to 2 or higher before onset; severe neurologic deficit (National Institutes of Health Stroke Scale [NIHSS]: ≥23) before edaravone treatment; history of cerebral infarction within 3 months; complicated with intracranial hemorrhage; and showing marked improvement in neurologic symptoms and signs, with a high probability of transient ischemic attack.

Therapy for AIS

Registered patients were treated with edaravone alone or edaravone + tPA depending on their clinical condition and the time of arrival at the hospital in PROTECT4.5. A 30-mg dose of edaravone was diluted with saline and administered twice daily in the morning and late afternoon by intravenous infusion for 30 minutes, for several days. The tPA (alteplase) was administered at a dose of .6 mg/kg according to the dosage regimen approved in Japan (10% of dose was given by rapid intravenous injection; the rest was given by intravenous infusion for 1 hour).

Study Assessments

The patients with AIS treated with edaravone alone or edaravone + tPA were sub-categorized according to their complications of DM, HT, or AF. The following evaluations for the outcome of AIS were conducted by sub-categorized populations; (1) changes in NIHSS from baseline to 3 months after the onset, (2) incidence of acute exacerbation, defined as 2 points or more deterioration in NIHSS from baseline within 1 week after the onset, (3) proportion of the patients with favorable outcome (mRS: 0-1) or unfavorable outcome (mRS: 2-6) at 3 months after the onset, and (4) incidence of symptomatic intracranial hemorrhage (sICH) within 36 hours of the onset. In addition, the identification of independent risk factors for highly unfavorable outcome (mRS: 3-6) at 3 months after the onset was attempted.

Statistical Analysis

The categorical data were expressed in terms of number or percentage of patients. The data on continuous variables