Simultaneous Combined Intravenous Recombinant Tissue Plasminogen Activator and Endovascular Therapy for Hyperacute Middle Cerebral Artery M1 Occlusion

S. TOYOTA, S. SUGIURA, K. IWAISAKO

Center for Endovascular Neurosurgery, Osaka Neurological Institute; Osaka, Japan

Key words: thrombolysis, acute stroke, cerebral infarct, endovascular treatment, interventional neuroradiology

Summary

We investigated the efficacy and safety of combined intravenous (IV) recombinant tissue plasminogen activator (rtPA) and simultaneous endovascular therapy (ET) for hyperacute middle cerebral artery (MCA) M1 occlusion.

Between October 2005 and April 2007, in the combined group, 22 patients eligible for IV rtPA, who were diagnosed as having MCA M1 occlusion, were treated with IV rtPA and simultaneous ET was initiated as soon as possible. The other patients were treated with IV rtPA alone (IV group A: $n = 11$). Between May 2007 and November 2008, all patients eligible for IV rtPA, who were diagnosed as having MCA M1 occlusion, underwent thrombolysis by IV rtPA alone (IV group B: $n = 24$).

The improvement of the National Institutes of Health Stroke Scale score at 24 hours was highest in the combined group (10 ± 4.1). In contrast, it was 5.1 ± 4.7 in the IV group A ($P = 0.017$) and 5.6 ± 5.6 in IV group B ($P = 0.006$). In the combined group, successful recanalization was observed in 18 of 22 patients with one symptomatic intracranial hemorrhage. The rate of mRS0-2 at three months was highest in the combined group, 36% in the IV group A and 33% in the IV group B ($P = 0.008$).

Simultaneous treatment with IV rtPA and ET improved the clinical outcome of MCA M1 occlusion without a significant increase of adverse effects in our study.

Introduction

Early thrombolytic therapy by intravenous (IV) recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke within three hours of onset has been shown to be effective if a certain number of inclusion criteria are met¹. However, particularly in major arterial occlusions, the rate of early recanalization with IV rtPA alone is low, approximately 30% of occluded proximal middle cerebral arteries (MCA)²⁻⁴.

Endovascular therapy (ET), such as intra-arterial thrombolysis, percutaneous transluminal angioplasty (PTA) and thrombectomy, is reported to have higher recanalization rates than IV rtPA alone, though they have the disadvantage of a longer delay to start recanalization treatment^{5,6}.

On the basis of combining the merits of IV and intra-arterial approaches, combination therapy using IV rtPA and ET has been reported in several studies⁷⁻¹². However, in most studies, additional ET was performed after the ineffectiveness of IV rtPA was confirmed. As a result, the start of ET was delayed by IV rtPA for one to two hours.

This delay may waste valuable time for rescuing ischemic penumbra^{13,14}. In this study, we investigated the efficacy and safety of combined therapy with IV rtPA and simultaneous ET for MCA M1 occlusion within three hours of onset.

Materials and Methods

Patient Selection

Between October 2005 and April 2007, we prospectively enrolled consecutive patients with acute ischemic stroke who were diagnosed as having acute MCA M1 occlusion and who underwent thrombolysis within three hours of onset. Patients were treated by combined therapy when they met the inclusion criteria for combined therapy (combined group) and were treated with IV rtPA alone when they did not meet these criteria (IV group A). The protocol was approved by our institutional committee, and informed consent was obtained from the patients' families. Between May 2007 and November 2008, all patients eligible for IV rtPA, who were diagnosed as having MCA M1 occlusion, underwent thrombolysis by IV rtPA alone (IV group B). The flowchart is shown in Figure 1.

The inclusion criteria were 18 years of age or older, presenting within three hours after onset of acute neurologic signs in the MCA distribution (hemiparesis, aphasia, unilateral spatial neglect, or conjugate deviation to the ischemic side), normal or slight early CT signs (less than one third of the MCA territory) on brain CT scans without evidence of hemorrhage, and MCA M1 occlusion diagnosed by angiography or magnetic resonance (MR) angiography. Additional inclusion criteria for combined therapy were planned initiation of ET within three hours of onset and obtaining informed consent for combined therapy.

The exclusion criteria corresponded to the Japanese guidelines for IV rtPA¹⁵, based on those of the National Institute of Neurological Disorders and Stroke rtPA trial¹: seizure at onset; rapidly improving neurologic signs at any point before thrombolysis; active bleeding; a history of intracranial hemorrhage; a history of symptomatic ischemic stroke, cerebrospinal surgery, or head trauma within 90 days; a history of gastrointestinal or urinary tract bleeding within 21 days; a history of major surgery within 14 days; diagnosis of neoplasm, aneurysm, Moyamoya disease, or arteriovenous malformation; severe hepatic insufficiency; acute pancreatitis; uncontrolled hypertension defined by systolic blood pressure of more than 185 mm Hg or diastolic blood pressure of more than 110 mm Hg despite bolus administration of antihypertensive drugs; baseline international normalized ratio of prothrombin time greater than 1.7;

activated partial thromboplastin time more than 1.5 times the normal time; baseline platelet count less than 100,000/mm³; or glucose concentration of less than 2.7 mmol/L or more than 22.2 mmol/L. An additional exclusion criterion for combined therapy was difficult access to MCA with vessel abnormality.

Thrombolytic and Endovascular Therapy

When a patient was considered a candidate for thrombolysis as a result of head CT scan, edaravone, a free radical scavenger approved in Japan¹⁶, was immediately administered. Patients meeting the inclusion criteria for combined therapy underwent immediate cerebral angiography. In order to avoid bleeding complications from the puncture site for placement of the sheath into the femoral artery, we placed the sheath before IV rtPA in our study. Just after a 6F sheath was placed into the femoral artery, IV rtPA (alteplase, 0.6 mg/kg, 60 mg maximum) was started with a 10% loading bolus injection for 1 minute followed by continuous infusion for 60 minutes (1.5% of 0.6 mg/kg per minute, 1 mg/ml). When a thrombus was identified in the M1 portion of the MCA, ET was initiated immediately without discontinuing IV rtPA for 60 minutes. After the microcatheter (Renegade; Boston Scientific, Fremont, CA, USA) was passed over the micro-guidewire (Transend EX; Boston Scientific) through the occlusive thrombus, 2 mg rtPA (1 mg/ml) was manually injected for two minutes through the catheter beyond the thrombus. When the catheter was retracted into the thrombus, manual injection of rtPA was made directly into the thrombus as well as to the proximal site of the thrombus. If recanalization of the M1 portion was not achieved after several applications of intra-arterial rtPA and mechanical thrombus disruption using a microguidewire, percutaneous transluminal angioplasty (PTA) was added. The PTA balloon (Gateway, 2 mm in diameter and 9 mm in length; Boston Scientific) was inflated for 30 or 60 seconds at 4 or 6 atm repeatedly until recanalization was obtained. When distal embolization was observed, intra-arterial rtPA was added. In all cases, the maximum dose of rtPA injected intra-arterially did not exceed 10 mg. ET was terminated if successful recanalization was achieved as defined in the following section. The second condition for termination of treatment was extravasation of contrast suggesting vessel rupture, or 120 minutes

of ET. In patients with vessel abnormality that made access to MCA difficult, or those who did not meet the inclusion criteria for combined therapy, only IV rtPA (0.6 mg/kg) was performed, as IV group A. In general, additional anticoagulation or antiplatelet therapy was initiated 24 hours after thrombolysis, respectively, for patients with cardioembolic (CE) or atherothrombotic (AT) stroke without intracranial hemorrhagic transformation/intracerebral hemorrhage (ICH).

Neuroradiologic Evaluation

The occlusion sites of MCA were diagnosed by angiography or MR angiography, as MCA M1 proximal or M1 distal. Recanalization after ET was evaluated by the thrombolysis in myocardial Infarction (TIMI) grade¹⁷. In brief, the absence of recanalization was regarded as TIMI grade 0, minimal as grade 1, partial as grade 2, and complete as grade 3. Successful recanalization was defined as achieving TIMI 2 or 3 flow in all M1 and M2 segments.

Outcome Measures

Clinical assessments included the National Institutes of Health Stroke Scale (NIHSS) scores at baseline and at 24 hours, modified Rankin Scale (mRS) scores and mortality at three months, the rate of successful recanalization at completion of ET, and symptomatic and asymptomatic ICH (including hemorrhagic infarction, parenchymal hematoma, and subarachnoid hemorrhage) during the first 36 hours after thrombolysis. Symptomatic ICH was de-

fined as that accompanied by ≥ 4 NIHSS point worsening.

Statistical Analysis

All values are expressed as the mean $\pm$ SD. All statistical analyses were performed using the SPSS software package (SPSS 15; SPSS Inc.). Categorized variables among 3 groups were analyzed using the Kruskal-Wallis test, and differences between individual subgroups were compared using the Mann-Whitney test. Continuous variables among the three groups were analyzed using ANOVA, and differences between individual subgroups were compared using the Scheffe test. Differences between NIHSS at baseline and at 24 hours were compared using the paired *t*-test. A *P* value of < 0.05 was considered significant.

Results

Demographic Data

Fifty-seven patients aged 72 ± 9.4 years were enrolled. Between October 2005 and April 2007, 22 patients were treated with simultaneous combined therapy (combined group) and 11 with IV rtPA alone (IV group A), including two patients showing vessel abnormality that made access to MCA difficult. Between May 2007 and November 2008, 24 patients were treated with IV rtPA alone (IV group B).

The baseline clinical characteristics are presented in Table 1. There was no significant difference among the 3 groups with regard to age

Table 1 Main characteristics of 31 patients with symptomatic unilateral and bilateral carotid artery lesions

	Combined group	IV group A	IV group B	P value
Age (years)	69+/-8.1	74+/-10	73+/-9.5	0.197
Male (%)	55	45	50	0.882
Hypertension (%)	73	45	71	0.255
Diabetes mellitus (%)	18	9.1	21	0.97
Dyslipidemia (%)	18	18	21	0.699
Atrial fibrillation (%)	77	82	75	0.907
Smoking (%)	41	27	46	0.587
Baseline NIHSS score	17+/-2.8	16+/-2.3	16+/-4.4	0.498
M1 proximal occlusion (%)	59	55	54	0.939

P value from Kruskal Wallis test comparing categorized variables among three groups.
P value from ANOVA comparing continuous variables among three groups.

($P = 0.197$) or sex ($P = 0.882$). There was no significant difference among the three groups with regard to risk factors, including hypertension ($P = 0.255$), diabetes ($P = 0.97$), dyslipidemia ($P = 0.699$), atrial fibrillation ($P = 0.907$) or smoking ($P = 0.587$). Most of the patients were diagnosed as having a cardioembolic stroke, 77 % in the combined group, 88% in IV group A and 75% in IV group B, with no significant difference ($P = 0.907$).

The baseline NIHSS score was 17 ± 2.8 in the combined group, 16 ± 2.3 in IV group A, and 16 ± 4.4 in IV group B, and there was no significant difference among the 3 groups ($P = 0.498$). In the combined group, baseline NIHSS was 18 ± 2.2 in CE group and 16 ± 4.4 in AT group, with no significant difference between groups.

There was no significant difference among the three groups with regard to the interval from onset to the emergency department ($P = 0.483$) and initiation of IV rtPA ($P = 0.558$).

In the combined group, sites of occlusion diagnosed by angiography were M1 proximal ($n = 13$), M1 distal ($n = 9$). In the IV A group, occlusion sites diagnosed by angiography or MRA were M1 proximal ($n = 6$), M1 distal ($n = 5$), and in the IV B group, M1 proximal ($n = 13$) and M1 distal ($n = 11$). There was no significant difference among the three groups ($P = 0.939$).

The mean intervals from onset to IV rtPA

were 106 ± 23 minutes in the combined group, 112 ± 32 minutes in IV group A and 113 ± 20 minutes in IV group B, with no significant difference among the three groups ($P = 0.558$).

Arterial Recanalization

The mean intervals from onset to intra-arterial rtPA and to termination of ET were 151 ± 33 and 210 ± 41 minutes, respectively (Table 2). The time lag between IV and intra-arterial rtPA was 46 ± 26 minutes, during which arterial occlusions persisted after the initiation of IV rtPA in all 22 patients. In the combined group, 11 patients were treated with PTA. The dose of intra-arterial rtPA was 5.9 ± 2.2 mg (range, 2–10 mg). At the end of ET, successful recanalization (TIMI 2, 3) was observed in 18 (82 %). The successful recanalization rate was 82% in CE group and 80% in AT group, with no significant difference between groups.

In IV group B, the successful recanalization rate 24 hours after treatment was 38%.

Clinical Outcome and Safety

In all groups, significant neurologic improvement was observed at 24 hours. The improvement of the NIHSS score at 24 hours was highest in the combined group (10 ± 4.1), 5.1 ± 4.7

Table 2 Interval from onset to treatment.

	Combined group	IV group A	IV group B	P value
Onset				
To emergency department (min)	53 ± 18	62 ± 25	55 ± 23	0.483
To IV rtPA (min)	106 ± 23	112 ± 32	113 ± 20	0.558
To IA rtPA (min)	151 ± 33			
Delay between IV and IA (min)	46 ± 26			

P value from ANOVA comparing three groups.

Table 3 Clinical outcomes.

	Combined group	IV group A	IV group B	P value
Baseline NIHSS	17 ± 2.8	16 ± 2.3	16 ± 4.4	0.498
NIHSS at 24h	6.8 ± 4.7	11 ± 5.9	11 ± 6.6	0.049
Improvement of NIHSS	10 ± 4.1	$5.1 \pm 4.7^*$	$5.6 \pm 5.6^*$	0.002
mRS0-1 at 3 month (%)	54.5	27.3	25	0.093
mRS0-2 at 3 month (%)	72.7	36.4	33.3#	0.02

P value from ANOVA comparing NIHSS among three groups.
P value from Kruskal Wallis test comparing the proportion of mRS among three groups.
** significant difference from the combined group using the Scheffe test.*
significant difference from the combined group using the Mann-Whitney test.

Figure 1 Thrombolysis flowchart.

in IV group A ($P = 0.017$) and 5.6 ± 5.6 in IV group B ($P = 0.006$), significantly (Table 3). In the combined group, the improvement of the NIHSS score at 24 hours was 11 ± 4.6 in CE group and 9.6 ± 1.7 in AT group, with no significant difference between groups.

The proportion of patients showing mRS0-1 at three months was 55% (12 patients) in the combined group, 27% (three patients) in IV group A, and 25% (six patients) in IV group B. The proportion of patients showing mRS0-2 at three months was 73% (16 patients) in the combined group, 36% (four patients) in IV group A, and 33% (eight patients) in IV group B. The proportion in the combined group was significantly higher than in IV group B ($P = 0.008$) (Figure 2, Table 3). In the combined group, the proportion of mRS0-1 at three months was 53% in CE group and 60% in AT group. The proportion of mRS0-2 at three months was 71% in CE group and 80% in AT group, with no significant difference between groups.

Figure 2 mRS at 3 months. The proportion of mRS0-2 in the combined group was significantly higher than in IV group B using the Mann-Whitney test ($P = 0.008$).

There were three asymptomatic ICHs, and one symptomatic ICH at 36 hours in the combined group. These 4 ICHs were not procedural. In IV group A, there were two asymptomatic ICHs, and one symptomatic ICH. In IV group B, there were four asymptomatic ICHs, and one symptomatic ICH. There were no other hemorrhagic complications, such as groin or retroperitoneal hematoma, in any group. One patient in the combined group, one in IV group A and one in IV group B died.

Discussion

Although the efficacy and safety of IV rtPA within three hours of stroke onset were confirmed, it did not always lead to favorable outcomes in a considerable proportion of patients^{1,15,18}, mainly because of a low-recanalization rate of major arterial occlusions. Especially in MCA M1 occlusion, the rate of early recanalization and the proportion of patients showing a favorable outcome by IV rtPA alone are low²⁻⁴. After IV rtPA alone for patients with M1 occlusion, Wolpert et al. reported recanalization in 12 of 33 (36%) patients evaluated with cerebral angiography⁴; and Neumann-Haefelin et al. reported recanalization in 20 of 52 (38%) patients evaluated with MRA². Saqqur et al. reported complete recanalization within two hours from the onset of IV rtPA treatment alone in 49 of 163 (30%) patients evaluated with transcranial Doppler, and the proportion of patients showing mRS0-1 at three months was only 25% (33 in 131)³. In our series, the clinical outcome of IV rtPA treatment alone was similarly unfavorable to this study: the proportion of patients showing mRS0-1 at three months was 27% in IV group A and 25% in IV group B.

On the other hand, endovascular therapy (ET) is reported to have higher recanalization rates than IV rtPA alone. In the prolyse in acute cerebral thromboembolism (PROACT) II trial, 66% of patients treated with intra-arterial prourokinase within six hours of onset had partial or complete recanalization⁵. In the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan, 74% of patients treated with intra-arterial infusion of urokinase with stroke within six hours of onset had partial or complete recanalization⁶. Only 26% recovered to the level of mRS0, one at 90 days in the PROACT II trial and 42% in MELT

Japan, although they included not only M1 occlusion but also M2 occlusion. The outcomes of both trials are not always much better than that of Saqqur et al. who reported that the proportion of patients showing mRS0-1 at three months was 25% in proximal MCA occlusion and 52% in distal MCA occlusion with IV rtPA treatment alone³. We think that the outcomes of intra-arterial approaches may be affected by the disadvantage of a long delay to starting treatment for recanalization; the interval from onset to ET was 318 minutes in PROACT II trial⁵, and 227 minutes in MELT Japan⁶.

On the basis of combining the merits of IV and intra-arterial approaches, combination therapy using IV rtPA and ET has been expected, especially in major arterial occlusions. Some studies have demonstrated that combination therapy of IV rtPA and ET has higher recanalization rates than IV rtPA alone^{7-12,19-22}. In the interventional management of stroke (IMS) I study, additional intra-arterial rtPA was administered after IV rtPA in patients with acute ischemic stroke⁸. In the interventional management of stroke (IMS) II study, IV rtPA and intended intra-arterial rtPA via an EKOS sonography-activated microinfusion catheter was combined⁷. The recanalization rate was 56% in the IMS I study⁸, and 73% at the end of the procedure in EKOS-treated subjects⁷. In the IV tPA group of multi mechanical embolus removal in cerebral ischemia (MERCI) trial, mechanical embolectomy with the Merci Retriever was performed in patients with acute ischemic stroke after IV tPA failure, and intra-arterial injection of tPA were allowed in cases of treatment failure with the device within eight hours of symptom onset. The recanalization rate in the IV tPA group of the Multi MERCI trial was 73%¹¹. Despite the high-recanalization rate of combination therapy of IV rtPA and ET, the outcome was not always excellent. The proportion of mRS0-1 at three months was 30% in the IMS I study⁸ and 33% in the IMS II study⁷ and the proportion of mRS0-2 at three months was 35% in the IV tPA group of the multi MERCI trial¹¹. Although Shaltoni et al. reported that intra-arterial thrombolysis was safe and feasible after full-dose IV rtPA therapy for acute ischemic stroke⁹, Singer et al. demonstrated that combination therapy of IV rtPA and intra-arterial rtPA are associated with an increased symptomatic ICH risk (20%) as compared to IV rtPA alone (5%)¹⁰.

However, we should keep in mind that in most studies of the combination therapy of IV rtPA and ET, additional intra-arterial therapy was performed after the ineffectiveness of IV rtPA was confirmed^{7,8,11}. Therefore, the initiation of the intra-arterial procedure was delayed from the onset of stroke. The delay from onset to intra-arterial rtPA was 217 minutes in the IMS I study⁸, and that from onset to device treatment was 3.6 hours in the IV tPA group in the multi MERCI trial¹¹. We think that waiting until confirming whether recanalization by IV rtPA was successful might waste valuable time for rescuing ischemic penumbra. The delay increases not only the infarction volume¹⁴, but also the risk of reperfusion injury, including hemorrhagic infarction and malignant space-occupying brain edema^{10,23}. Our treatment strategy is essentially different from those performed previously^{7,8,11}, because it is a combination of IV rtPA and intentional simultaneous ET as primary therapy. Our strategy of simultaneous treatment aims to minimize the delay from onset to the intra-arterial procedure in order to rescue neuronal tissue as much as possible¹². The delay from onset to intra-arterial rtPA was 151 minutes in the present study, much shorter than in those performed previously. We think that the minimum delay in the present study could increase the early recanalization rate, and rescue brain tissue as much as possible, compared to the combined therapy reported previously. In the present study, successful recanalization was observed in 82%, and the proportion of patients showing mRS0-2 at three months was 73%, which were more favorable than the combined therapy reported previously. Early recanalization might also reduce the occurrence of reperfusion injury, including symptomatic ICH, because it could be achieved when disruption of the blood-brain barrier was minimal²⁴.

Using our strategy of simultaneous treatment with IV rtPA and ET, it is possible that an unnecessary intra-arterial procedure may be performed on patients who would have improved by IV rtPA alone. It is difficult to standardize the system of simultaneous treatment with IV rtPA and ET, and it may be available only at high-volume stroke centers, because our procedure of simultaneous treatment is labor intensive. However, in view of the poor rate of early recanalization by IV rtPA alone, as well as the risk for a poor outcome, such as severe disability or death if early recanalization is not achieved, ET, which is relatively safe when per-

formed by trained interventional neuroradiologists, might be beneficial and justified in patients with major arterial occlusions who are transferred to high-volume stroke centers within one to two hours after onset¹².

Our study has some limitations. The IV group A was biased because it included patients excluded from the combined group, and IV group B was a historical control group, even though the treatment protocol was identical to the combined group, except ET. We also could not directly compare the recanalization rate in each group because we did not have the full protocol to evaluate recanalization by MRA. Additional randomized studies which include the full protocol to evaluate recanalization by MRA will be required to confirm our results.

In this study, we decided on IV rtPA treatment based on brain CT scans on admission according to the Japanese guidelines for IV rtPA¹⁵, based on those of the National Institute of Neurological Disorders and Stroke rtPA trial¹. We could evaluate the degree of brain damage in detail if we had the protocol to utilize a CT scoring system, such as the Alberta Stroke Program Early CT Score (ASPECTS)²¹ or MR diffusion imaging^{2,18} in this study. With our method of mechanical thrombus disruption with a microguidewire and a PTA balloon, which were used without arrest of antegrade blood flow, fragments of the thrombus might be dislodged downstream, resulting in distal embolism when the clot volume was large. Therefore, we think that it is better to utilize a retrieval system, such as Merci Retriever, which was not available in Japan, designed to allow embolectomy with arrest of antegrade blood flow¹¹.

In order to avoid bleeding complications from the puncture site with placement of the sheath into the femoral artery, we placed the sheath before IV rtPA in our study; however, this procedure might delay the start of systemic treatment by IV rtPA. The delay should be minimal because loss of time can be crucial for patient outcome. In order to reduce the loss of time, starting IV rtPA before sheath placement might be reasonable; however, in our hospital, the time-limiting steps to start of systemic treatment by IV rtPA were usually checking the blood examination results, including a coagulation test, complete blood count and blood chemistry study, or obtaining informed consent from the patients' families. Because the time for transferring patients to the system for cerebral angiography was very short in our hospital,

the time to start IV rtPA did not demonstrate much difference among the combined group and IV group A and IV group B, as shown in Table 2.

The delay of 46 ± 26 minutes to intra-arterial rtPA application was not short enough, but we think that the time is necessary to perform the ET procedure safely.

It is possible that our results were influenced by the neuroprotective effect of Edarabon, a

free radical scavenger, because it could reduce the reperfusion injury, as reported previously¹⁶.

Conclusion

Simultaneous treatment with IV rtPA and ET improved the clinical outcome of MCA M1 occlusion without a significant increase of adverse effects in our study.

References

- 1 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995; 333: 1581-1587.
- 2 Neumann-Haefelin T, du Mesnil de Rochemont R, Fiebach JB, et al. Effect of incomplete (spontaneous and postthrombolytic) recanalization after middle cerebral artery occlusion: a magnetic resonance imaging study. *Stroke* 2004; 35: 109-114.
- 3 Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007; 38: 948-954.
- 4 Wolpert SM, Bruckmann H, Greenlee R, et al. Neuro-radiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *Am J Neuroradiol* 1993; 14: 3-13.
- 5 Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism*. *J Am Med Asso*. 1999; 282: 2003-2011.
- 6 Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007; 38: 2633-2639.
- 7 IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. *Stroke*. 2007; 38: 2127-2135.
- 8 IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke*. 2004; 35: 904-911.
- 9 Shaltoni HM, Albright KC, Gonzales NR, et al. Is intra-arterial thrombolysis safe after full-dose intravenous recombinant tissue plasminogen activator for acute ischemic stroke? *Stroke*. 2007; 38: 80-84.
- 10 Singer OC, Berkefeld J, Lorenz MW, et al. Risk of symptomatic intracerebral hemorrhage in patients treated with intra-arterial thrombolysis. *Cerebrovasc Dis*. 2009; 27: 368-374.
- 11 Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *Am J Neuroradiol*. 2006; 27: 1177-1182.
- 12 Sugiura S, Iwaisako K, Toyota S, Takimoto H. Simultaneous treatment with intravenous recombinant tissue plasminogen activator and endovascular therapy for acute ischemic stroke within 3 hours of onset. *Am J Neuroradiol*. 2008; 29: 1061-1066.
- 13 Heiss WD. Ischemic penumbra: evidence from functional imaging in man. *J Cereb Blood Flow Metab*. 2000; 20: 1276-1293.
- 14 Heiss WD, Kracht L, Grond M, et al. Early [(11)C] Flumazenil/H(2)O positron emission tomography predicts irreversible ischemic cortical damage in stroke patients receiving acute thrombolytic therapy. *Stroke*. 2000; 31: 366-369.
- 15 Yamaguchi T, Mori E, Minematsu K, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke*. 2006; 37: 1810-1815.
- 16 Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis*. 2003; 15: 222-229.
- 17 TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med*. 1985; 312: 932-936.
- 18 Delgado-Mederos R, Rovira A, Alvarez-Sabin J, et al. Speed of tPA-induced clot lysis predicts DWI lesion evolution in acute stroke. *Stroke*. 2007; 38: 955-960.
- 19 Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. *Stroke*. 1999; 30: 2598-2605.
- 20 Ernst R, Pancioli A, Tomsick T, et al. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. *Stroke*. 2000; 31: 2552-2557.
- 21 Hill MD, Barber PA, Demchuk AM, et al. Acute intravenous-intra-arterial revascularization therapy for severe ischemic stroke. *Stroke*. 2002; 33: 279-282.
- 22 Lee KY, Kim DI, Kim SH, et al. Sequential combination of intravenous recombinant tissue plasminogen activator and intra-arterial urokinase in acute ischemic stroke. *Am J Neuroradiol*. 2004; 25: 1470-1475.
- 23 Rudolf J, Grond M, Stenzel C, et al. Incidence of space-occupying brain edema following systemic thrombolysis of acute supratentorial ischemia. *Cerebrovasc Dis*. 1998; 8: 166-171.
- 24 Montaner J, Molina CA, Monasterio J, et al. Matrix metalloproteinase-9 pretreatment level predicts intracranial hemorrhagic complications after thrombolysis in human stroke. *Circulation*. 2003; 107: 598-603.

Shingo Toyota, MD
Center for Endovascular Neurosurgery
Osaka Neurological Institute
2-6-23 Shounai, Takara-machi, Toyonaka
Osaka 561-0836, Japan
Tel.: +81-6-6333-0080 - Fax: +81-6-6333-7611
E-mail: stshto@aol.com