**Multicenter study of intravenous recombinant tissue plasminogen
activator infusion around Hiroshima, Japan
–HARP Registry Study–**

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Disclosures

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Running title: Multicenter study of IV rtPA around Hiroshima

Abstract

Objective: Approximately ten years have passed since intravenous (IV) recombinant tissue plasminogen activator (rtPA) therapy was approved in Japan. The aim of this retrospective study was to identify the effectiveness and safety of IV alteplase therapy with the Japanese original dose around Hiroshima via consideration of the patients' backgrounds, examination findings, and outcomes. **Methods:** All consecutive ischemic stroke patients who received IV alteplase therapy between October 2005 and October 2010 were registered, and statistical analysis was performed. **Results:** Four hundred twenty-nine ischemic stroke patients (172 female [40.1%], mean age 73.7±11.8 years) were registered. The proportion of patients over 75 years old was 51.5% (221 patients). The median NIH Stroke Scale (NIHSS) scores at admission were 13 (interquartile range [IQR], 9–19), and the NIHSS scores 24 hours after alteplase infusion were 8 (IQR, 3–15). The proportion of intracerebral hemorrhage within the initial 36 hours was 20.2% (86 patients). After the multivariate regression analysis, a previous history of hypertension (Odds Ratio [OR] 4.14, 95% confidence interval [CI] 1.32–14.79, $p=0.01$) and no recanalization (OR 10.10, 95%CI 3.03–39.33, $p<0.0001$) were independently associated with a modified Rankin Scale (m-RS) score ≥ 2 at 3 months. Patients over 75 years old were not significantly associated to an intracerebral hemorrhage within the initial 36 hours and an m-RS score ≥ 2 at 3 months. **Conclusions:** The results of our study demonstrated that IV alteplase therapy with the Japanese original dose was effective and

exhibited a safety profile similar to other studies. We should not hesitate to IV alteplase therapy simply because of advanced age.

Introduction

Approximately ten years have passed since intravenous (IV) recombinant tissue plasminogen activator (rtPA) therapy was approved in Japan. The efficacy and safety of the Japanese original low-dose (0.6 mg/kg) IV alteplase have been demonstrated in previous studies.^{1,2} In addition, the administration time of alteplase has been increased to within 4.5 hours of stroke onset since August 31st 2012 in Japan; thus, an increase in alteplase therapy is also expected.

However, limitations of IV alteplase therapy have been identified especially in cases that involve occlusion of the internal carotid artery or proximal middle cerebral artery.^{3,4} Mechanical thrombectomy was first performed in 2010, and it has been effective in cases refractory to IV alteplase therapy.⁵⁻⁷ To perform high-quality stroke therapy under conditions in which the treatment approach dynamically changes, the continued review of large clinical case series is necessary. Furthermore, because Japan has still been advancing its super-aging society, it is important to clarify the characteristics of these cases in difference in age. The risk of IV alteplase therapy for elderly patients remains controversial.

Thus, we performed a multicenter study (Hiroshima Acute stroke Retrospective and Prospective [HARP] Registry Study) to clarify the characteristics of acute stroke patients around Hiroshima, Japan. The aim of this retrospective study was to identify the effectiveness and safety of IV alteplase therapy with the Japanese original dose around Hiroshima via

consideration of the patients' backgrounds, examination findings, and outcomes.

Patients and Methods

The HARP Study Group was composed of 7 Japanese stroke centers located around Hiroshima, Japan. All consecutive ischemic stroke patients who received IV alteplase therapy between October 2005 and October 2010 were registered. Patient eligibility for alteplase therapy was primarily determined based on the Japanese guidelines for IV alteplase therapy, which follow the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study⁸ and Japan Alteplase Clinical Trial (J-ACT).⁹

Each patient received a single alteplase dose of 0.6 mg/kg IV with 10% administered as a bolus within 3 hours of stroke onset, followed by a continuous IV infusion of the remaining drug over 1 hour. The use of an antithrombotic agent was prohibited for 24 hours after stroke onset, blood pressure was maintained at <180/105 mmHg, and neurological signs and symptoms were frequently monitored. Prior to alteplase therapy, all patients underwent computed tomography (CT) or magnetic resonance imaging (MRI). The stroke subtype was determined based on CT or MRI findings, electrocardiography, and carotid artery and cardiac ultrasound findings by at least two stroke specialists according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.¹⁰ Recanalization was assessed by

the MR angiography 24 hours after alteplase infusion and was graded as complete, partial, or no recanalization as follows: (1) complete recanalization, which indicated reappearance of the entire occluded artery and the distal branch of the vessels; (2) partial recanalization, which indicated restoration of part of the distal vessel supplied by the occluded artery; and (3) no recanalization, which indicated persistent occlusion. Recanalization was defined as complete or partial recanalization. Intracerebral hemorrhage (ICH) was defined as CT evidence of new ICH within the initial 36 hours. White matter lesions (WMLs) were graded as the degree of severity of the WMLs via visual inspection using the Fazekas classification of WMLs as follows: none (grade 0), punctate (grade 1), early confluent (grade 2), and confluent (grade 3) lesions.¹¹ The neurological severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) at admission and 24 hours after alteplase infusion.¹² The patients' clinical outcomes were evaluated with the modified Rankin scale (m-RS) at discharge and 3 months after stroke onset.¹³ A favorable outcome was defined as an m-RS score of 0–1 at 3 months after stroke onset. The study was approved by the Institutional Review Board (IRB) of each institute.

Hypertension was defined as the use of anti-hypertensive medicines prior to admission or a confirmed blood pressure $\geq 140/90$ mmHg at rest 2 weeks after stroke onset. Diabetes mellitus was defined as an HbA1c of $\geq 6.5\%$, a fasting blood sugar ≥ 126 mg/dl, or the use of anti-diabetic medicines. Hyperlipidemia was defined as a total cholesterol (T-chol) ≥ 220 mg/dl, a

low-density lipoprotein cholesterol (LDL-chol) ≥ 140 mg/dl at admission, or the use of anti-hyperlipidemia medications. Atrial fibrillation was diagnosed based on electrocardiographic findings at admission or during hospitalization or a previous history of atrial fibrillation.

Statistical analysis was performed using JMP 11.2 statistical software (SAS Institute, Inc., Cary, North Carolina, USA). The data are presented as the mean $\pm$ SD or the median (minimum–maximum) for continuous variables. Statistical analyses for the comparisons of the two groups were performed using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. P-values <0.05 were considered statistically significant. Multivariate analyses were performed using a stepwise analysis to determine the predictors of an ICH within the initial 36 hours, and an m-RS score ≤ 1 at 3 months was based on the characteristics detailed in Tables 1 and 2. For each outcome, a backward selection procedure was performed using $p>0.10$ of the likelihood ratio test for exclusion.

Results

Four hundred twenty-nine ischemic stroke patients (172 female [40.1%], mean age 73.7 ± 11.8 years) were registered. Table 1 shows the baseline characteristics of all registered patients. There were 285 patients with hypertension (66.4%) and 220 patients with atrial fibrillation (51.3%). The leading stroke subtype was cardioembolism (59.4%) followed by large artery

atherosclerosis (24.0%). The median time between stroke onset and alteplase infusion was 135 minutes (interquartile range [IQR], 110–158). The median NIHSS scores at admission were 13 (IQR, 9–19), and the NIHSS scores 24 hours after alteplase infusion were 8 (IQR, 3–15).

The proportion of patients over 75 years old was 51.5% (221 patients). The proportion of female was significantly higher in patients over 75 years old than patients under 75 years old ($p<0.0001$). Patients over 75 years more commonly had hypertension ($p=0.02$), atrial fibrillation ($p<0.0001$), and previous history of stroke ($p=0.0004$) than those under 75 years old. NIHSS scores at admission were significantly higher in patients over 75 years old than those under 75 years old ($p<0.0001$).

Table 2 shows the imaging findings. In 355 (82.8%) out of 429 patients, the location of the occluded artery was identified. The leading site of the arterial occlusion was the middle cerebral artery (76.0%) followed by the internal carotid artery (13.5%). The recanalization of the occluded artery was assessed in 260 patients. One hundred fifty-seven patients exhibited complete or partial recanalization (60.4%). The proportion of ICH within the initial 36 hours was 20.2% (86 patients). Three hundred fifty-eight patients had MRI findings consistent with WMLs; 115 patients were grade 0 (32.1%), 140 patients were grade 1 (39.1%), 66 patients were grade 2 (18.4%), and 37 patients were grade 3 (10.3%). The severity of WMLs is higher in patients over 75 years old than in patients under 75 years old.

Based on the multivariate regression analysis using a backward selection

method, a previous history of atrial fibrillation (Odds Ratio (OR) 5.70, 95% confidence interval (CI) 1.93–20.44, $p=0.001$), the NIHSS score at admission (OR 1.06, 95%CI 1.01–1.11, $p=0.03$), and recanalization (OR 4.95, 95%CI 2.23–12.29, $p<0.0001$) were independently associated with ICH within the initial 36 hours (Table 3). The functional outcomes (m-RS) at 3 months were evaluated in 224 patients. One hundred patients (44.6%) had an m-RS score ≤ 1 at 3 months. When 33 patients with a premorbid m-RS score ≥ 2 were excluded from the analysis, 99 (51.9%) of 191 patients had an m-RS score ≤ 1 (Figure 1). The proportion of patients with an m-RS score ≤ 1 at 3 months was significantly lower in patients over 75 years old than patients under 75 years old ($p<0.0001$). After the multivariate regression analysis using a backward selection method, a previous history of hypertension (OR 4.14, 95%CI 1.32–14.79, $p=0.01$) and no recanalization (OR 10.10, 95%CI 3.03–39.33, $p<0.0001$) were independently associated with an m-RS score ≥ 2 at 3 months (Table 4).

Discussion

Our study identified the characteristics of patients who received IV rtPA therapy around Hiroshima, Japan. The leading site of arterial occlusion was the middle cerebral artery (76.0%) followed by the internal carotid artery (13.5%). The proportion of ICH within the initial 36 hours was 20.2%, whereas an m-RS score ≤ 1 at 3 months was 44.6%. These results were similar to previous reports that demonstrated the efficacy and safety of the

Japanese original low-dose (0.6 mg/kg) IV alteplase.^{1,2}

In this study, the mean age of the patients was 73.7±11.8 years, and the proportion of females was 40.1%. The previous Japanese low-dose (0.6 mg/kg) alteplase studies, the Japan post-Marketing Alteplase Registration Study (J-MARS)¹ and the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study² all demonstrated similar patient characteristics (J-MARS, 72 years, female 37.9%; SAMURAI, 72±12 years, female 37.2%). The proportions of the risk factors are also similar in these 3 studies. Therefore, we assume that the results of our study may reflect the characteristics of general Japanese ischemic stroke patients with IV alteplase treatment.

Focusing on the difference in age, the proportion of female, hypertension, atrial fibrillation, and previous history of stroke was significantly higher in patients over 75 years old than patients under 75 years old in this study. The outcomes of patients over 75 years old were poorer than those of patients 75 years old. These results are thought to be similar to previous alteplase studies.

Our study demonstrates that an ICH within the initial 36 hours is independently associated with a previous history of atrial fibrillation, the NIHSS score at admission, and recanalization with IV alteplase. Previous studies have reported that the predisposing ICH factors after thrombolysis included renal dysfunction,¹⁴ atrial fibrillation,¹⁴ post-thrombolysis blood pressure,¹⁵ and large baseline diffusion-weighted imaging (DWI) volumes.¹⁵

In this study, we did not evaluate the renal function or baseline DWI. However, the baseline DWI volumes were significantly associated with the NIHSS score at admission in the SAMURAI study.¹⁶ Thus, a high NIHSS score at admission may reflect large baseline DWI volumes in our study. Additionally, atrial fibrillation is strongly associated with cardioembolism, and cardioembolism is a predictive factor of early hemorrhagic transformation in acute ischemic stroke.¹⁷ A high NIHSS score at admission and recanalization are also related to cardioembolism, which may be the reason that these factors are independently associated with an ICH within the initial 36 hours.

The clinical outcome is an important endpoint after thrombolysis. Our study demonstrates that a previous history of hypertension and no recanalization are independently associated with an m-RS score >2 at 3 months. The SAMURAI study demonstrated that age, the NIHSS score at admission, glucose levels, internal carotid artery occlusion, ASPECTS on CT, and IV anti-hypertensive medications immediately prior to rtPA were associated with a m-RS score >2 at 3 months.² Additionally, J-ACT II demonstrated that no recanalization of the occluded artery by 24 hours after rtPA infusion was strongly associated with a poor outcome (OR 12.5, 95%CI 2.5–62.4, $p<0.001$).³ We suggest the results of our study are similar to these Japanese rtPA studies and reflect the actual acute ischemic stroke clinical practice in Japan.

Patients over 75 years old were not significantly associated to an ICH within

the initial 36 hours and an m-RS score >2 at 3 months in this study. Elderly patients who receive IV alteplase therapy were generically thought to be likely to occur with hemorrhagic transformation and have poor outcomes. However, a growing body of evidence in recent years is accumulating to demonstrate that IV alteplase therapy for elderly patients is relatively safe.^{18,19} Our results surely demonstrated that patients over 75 years old had poorer outcome than patients under 75 years old, but the proportion of good outcome was no different from other alteplase studies of all ages. Therefore, we should not hesitate to IV alteplase therapy simply because of advanced age.

This study has some limitations. First, because these are retrospectively collected data, some imaging findings and m-RS scores at 3 months are missing. In our study, only 44% of patients were obtained their clinical outcome (m-RS scores at 3 months). It may influence on our slight favorable result (m-RS 0-1, 51%) in comparison previous studies. Analyzing those patients with the data of outcome, they were relatively younger (70.5 ± 11.8 years) and lower NIHSS score at admission (11 [8-18]) than the patients in the previous Japanese alteplase studies (SAMURAI; 72 ± 12 years, 13 [7.3-19], J-MARS; 72 years, 15 [9-20]). We consider that those results may also influence on the favorable outcome of our study compared with the previous studies. Other backgrounds and imaging findings are almost similar to the previous studies. Second, because all patients in this study live around Hiroshima, Japan, we cannot exclude the possibility that a regional bias

exists. However, most of our results are similar to previous Japanese rtPA trials. Therefore, we assume that these limitations do not have a substantial influence on our results.

In conclusion, the results of the HARP Registry Study demonstrated that IV rtPA therapy with the Japanese original dose was effective and exhibited a safety profile similar to other studies. We should not hesitate to IV alteplase therapy simply because of advanced age. Further prospective studies are necessary to clarify the characteristics of the cases in each region.

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Figure legends

Figure 1. m-RS score at 3 months in the all patients, patients over 75 years old, and patients under 75 years old with premorbid m-RS 0-1.

Appendix: Participating HARP Registry Study Institutions

Brain attack Center Ota Memorial Hospital (Kazuhiro Takamatsu, Taisei Ota, Isao Inoue, Shihori Kitae, Atsushi Tsuchiya, Nobutoshi Morimoto, Shoko Nagotani, Yasuyuki Ota, Motonori Takamiya, Hayato Matsushima, Muneyuki Makawa, Yoshio Omote, Hiroki Fujii, Miyuki Okamoto, Satoshi Kubo, Kota Sato, Taijyun Yunoki, and Masaru Kuriyama), Osaka Neurosurgical Hospital (Hideo Ooyama, Yuzo Kuroda, Keita Moriwaki, Naofumi Isono, Taro Yamashita, Naoki Hayashi, Shigeki Sadahiro, and Naohiro Osaka), National Hospital Organization Kure Medical Center (Tsuyoshi Torii, Eiichi Ohnuki, Tomokazu Nishikawa, Ryo Shimomura, Yukari Shinozaki, Syuichiro Neshige, and Atsuo Yamada), Chugoku Rosai Hospital (Takeshi Kitamura, Hiromasa Toji, Hideo Terasawa, Shinya Yamaguchi, and Satoshi Kataoka), Suiseikai Kajikawa Hospital (Eiichi Nomura, Yasuyo Mimori, Yumiko Kaseda, Junko Ikeda, Hiromitsu Naka, Satomi Kushitani, Eiji Imamura, Juri Kitamura, and Shinichi Wakabayashi), National Hospital Organization Higashihiroshima Medical Center (Koichi Noda, Kazue Tajima, Tomohito Sugiura, Yoshio Murakami, Takeo Shishido,

and Yoshito Nagano), and Hiroshima University Hospital (Takemori Yamawaki, Hideshi Kawakami, Sadao Katayama, Toshiho Ohtsuki, Hiroshi Yamashita, Hirofumi Maruyama, Takafumi Miyachi, Tetsuya Takahashi, Takeshi Nakamura, Tomohiko Ohshita, Kazuhide Ochi, Masahiro Higaki, Naoki Matsuoka, Daisuke Matsuura, Nasanori Hiji, Hiroki Ueno, Keita Kondo, Hiromasa Fukuba, Yoshimasa Sueda, Yu Yamazaki, Michie, Miyoshi, Kayoko Ishihara, Aiko Ishihara, Tomoyuki Kono, Shiro Aoki, Takashi Kurashige, Tomoya Mukai, Teppei Kotozaki, Akiko Segawa, Ikuko Takeda, Masahiro Nakamori, Tomohisa Nezu, Eisuke Dohi, Takamichi Sugimoto, Yuki Hayashi, Mayu Sekine, Michihiro Kono, Naoyuki Hara, and Masayasu Matsumoto).

Table 1. Baseline Characteristics of the Patients

Factors	All patients (n=429)	Patients over 75 years old (n=221)	Patients under 75 years old (n=208)	p-value
Age, years	73.7±11.8	82.5±5.2	64.4±9.5	<0.0001
Gender, female	172 (40.1%)	118 (53.4%)	54 (26.0%)	<0.0001
Risk factors				
Hypertension	289 (66.4%)	160 (72.4%)	129 (62.0%)	0.02
Diabetes mellitus	80 (18.6%)	44 (19.9%)	36 (17.3%)	0.49
Hyperlipidemia	128 (29.8%)	60 (27.2%)	68 (32.7%)	0.21
Atrial fibrillation	220 (51.3%)	135 (61.1%)	85 (40.9%)	<0.0001
Previous stroke	93 (21.8%)	63 (28.5%)	30 (14.6%)	0.0004
Prestroke independence, m-RS 0-1	381 (88.8%)	182 (82.4%)	199 (95.7%)	<0.0001
Prior use of anticoagulants	57 (13.3%)	35 (15.8%)	22 (10.6%)	0.02
Prior use of antiplatelet medication	108 (25.2%)	70 (31.7%)	38 (18.3%)	0.002
Prior use of antihypertensives	228 (53.1%)	134 (60.6%)	94 (45.2%)	0.001
Prior use of statins	81 (18.9%)	46 (20.8%)	35 (16.8%)	0.29

Stroke subtype				0.0005
Cardioembolism	255 (59.4%)	152 (68.8%)	103 (49.5%)	
Large artery atherosclerosis	103 (24.0%)	46 (20.8%)	57 (27.4%)	
Small artery occlusion	15 (3.5%)	6 (2.7%)	9 (4.3%)	
Other mechanisms	56 (13.1%)	17 (7.7%)	39 (18.8%)	
NIHSS score at admission, median (IQR)	13 (9–19)	15 (10–21)	11 (8–16)	<0.0001
Stroke onset to treatment time, minutes	135 (110–158)	131 (110–155)	140 (110–160)	0.30
IV antihypertensives immediately prior to rtPA	80 (18.6%)	37 (16.7%)	43 (20.7%)	0.25
Systolic blood pressure, mmHg	159.7±31.2	158.8±26.5	160.7±35.1	0.63
Diastolic blood pressure, mmHg	87.7±20.6	83.5±16.1	91.6±23.4	0.002
Pulse rate, beat/minutes	80.8±19.4	79.3±18.1	82.3±20.6	0.24

Table 2. Patient Imaging Findings

Findings	All patients (n=429)	Patients over 75 years old (n=221)	Patients under 75 years old (n=208)	p-value
Occluded artery (n=341)				0.19
Middle cerebral artery	259 (76.0%)	142 (77.2%)	117 (74.5%)	
Internal carotid artery	46 (13.5%)	25 (13.6%)	21 (13.4%)	
Anterior cerebral artery	10 (2.9%)	7 (3.8%)	3 (1.9%)	
Basilar artery	10 (2.9%)	3 (1.6%)	7 (4.5%)	
Posterior cerebral artery	8 (2.3%)	4 (2.2%)	4 (2.6%)	
Vertebral artery	8 (2.3%)	3 (1.6%)	5 (3.2%)	
Occluded artery recanalization (n=260)	157 (60.4%)	79 (57.7%)	78 (63.4%)	0.34
ICH within the initial 36 hours	86 (20.2%)	52 (23.7%)	34 (16.5%)	0.06

White matter lesions	<0.0001		
(WMLs) (n=358)			
Grade 0	115	41	74
	(32.1%)	(22.3%)	(42.5%)
Grade 1	140	66	74
	(39.1%)	(35.9%)	(42.5%)
Grade 2	66	48	18
	(18.4%)	(26.1%)	(10.3%)
Grade 3	37	29	8
	(10.3%)	(15.7%)	(4.7%)

Table 3. Multivariate Logistic Regression Analysis of Factors Associated with ICH within the Initial 36 Hours

	OR	95%CI	p-value
Over 75 years old	1.18	0.57–2.47	0.66
Atrial fibrillation	5.70	1.93–20.44	0.001
Previous stroke	0.94	0.40–2.08	0.87
Cardioembolism	1.39	0.39–5.12	0.61
NIHSS score at admission, per 1-point increase	1.06	1.01–1.11	0.03
Recanalization	4.95	2.23–12.29	<0.0001

Table 4. Multivariate Logistic Regression Analysis of Factors Associated with an m-RS score >2 at 3 months

	OR	95%CI	p-value
Over 75 years old	2.58	0.82–8.54	0.11
Hypertension	4.14	1.32–14.79	0.01
NIHSS score at admission, per 1-point increase	1.08	0.99–1.19	0.06
IV antihypertensives immediately prior to rtPA	0.81	0.17–3.79	0.79
ICH within the initial 36 hours	2.68	0.58–12.89	0.20
Internal carotid artery occlusion	2.66	0.58–13.97	0.21
No recanalization	10.10	3.03–39.33	0.0001

Fig 1