

The Medicolegal Issue of Tissue Plasminogen Activator in Ischemic Stroke: A Review of Judiciary Decrees in Taiwan

Wei-Hsi Chen^{1,2,3}, Hung-Sheng Lin¹, Chien-I Chen⁴, Min-Shon Chou²,
Chia-Wei Liou¹, Shun-Sheng Chen¹, Stroke Center-CGMH/Kaohsiung

Abstract-

Purpose: Tissue plasminogen activator (tPA) was approved by the Food and Drug Administration for ischemic stroke treatment since 1996 at the United States of America and also 2002 at Taiwan. Since after it is strongly advertised for a promising benefit to early thrombolysis that is further echoed by a recommendation in clinical guidelines from multiple medical associations in worldwide. Because of an overwhelming data of positive benefit collected in the evidence-based medicine database, legal dispute subsequently occurs when tPA is failed to be administrated in appropriate time.

Methods: In order to elucidate the legal viewpoint for tPA used in ischemic stroke, a review of the domestic judiciary decrees regarding this issue was conducted. Cases in Taiwan were executed from the open access database of the Judicial Yuan, Taiwan. The background, legal dispute and judgment of each case were analyzed.

Results: Till August, 2010, there were 6 cases in Taiwan. All cases occurred after 2003. The causes of disputes were a loss of chance for thrombolysis due to a delay of diagnosis (4 cases, 67%) and a failure of thrombolytic treatment after a diagnosis of ischemic stroke (2 cases, 23%). All cases were presented to non-neurologists at initial. Five cases expired or terminated into vegetation before litigation.

Conclusion: A failure of early diagnosis or treatment after a diagnosis of ischemic stroke are important for medicolegal dispute in tPA usage, which is expected to become prevalent in Taiwan in future. A fatal or poor outcome may be a triggering factor for litigation. Therefore, an improvement of the knowledge and practice to increase early diagnosis of ischemic stroke is the key factor for reducing medicolegal issue regarding tPA use in ischemic stroke. This is particularly true for non-neurologist physicians.

Key Words: ischemic stroke, tissue plasminogen activator, non-neurologist, medical litigation, medical malpractice

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From the ¹Department of Neurology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, and College of Medicine, Chang Gung University, Kaohsiung, Taiwan. ²Graduate Institute of Technology and Law, National The First University of Technology and Science, Kaohsiung, Taiwan. ³Medical Regulation Committee, Taiwan Medical Association, Taipei, Taiwan. ⁴Department of Law, Kainan University, Taoyuan, Taiwan.

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Correspondence to: Wei-Hsi Chen, MD. Department of Neurology, Chang Gung Memorial Hospital, No. 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung 833, Taiwan.
E-mail: salemcwh@adm.cgmh.org.tw

INTRODUCTION

Tissue plasminogen activator (t-PA) is a serine protease catalyzing the conversion of plasminogen to plasmin that degrades nascent fibrin clot to promise the circulatory patency in vessels. At 1995 through DNA technology, Genetech, Inc. (San Francisco, USA) successfully manufactured recombinant t-PA (rt-PA; brand name: Alteplase; tradename: Activase) for medical utility. After a positive result of human trials completed in the United States of America (USA)⁽¹⁻³⁾, the Food and Drug Administration rapidly licensed a patent to Alteplase® at June 18, 1996 (patent number 4,766,075) and approved for “management of acute ischemic stroke in adults, for improving neurological recovery, and reducing the incidence of disability”⁽⁴⁾. National Institute of Neurological Disorders and Stroke also established appropriate clinical guidelines for practice. In Taiwan, Alteplase® was approved at 2002 and the Central Health Insurance Bureau has established strict regulations for usage⁽⁵⁻⁶⁾. Taiwan Stroke Society has already recommended her clinical guidelines for thrombolysis in ischemic stroke patients⁽⁷⁾.

Since then, a few rt-PAs were subsequently approved for thrombolytic treatment. However, disputes of their usage are increasingly reported after their marketing. Litigation subsequently occurs⁽⁸⁻¹⁰⁾. In USA, a misdiagnosis or delayed diagnosis of ischemic stroke that prevents the rt-PA usage is the leading cause of litigations. In other words, plaintiff claimed a loss of chance for rt-PA treatment in the majority of cases. About 15% of litigations are claimed for an injury from rt-PA administration⁽⁸⁻¹⁰⁾. These findings clearly suggest the importance of acting according to clinical guideline and inform consent in rt-PA treatment.

Regarding to Taiwan, there is still a shortage of a systematic review of the judiciary decree for rt-PA dispute. In order to reduce the risk of legal litigation, it is necessary to elucidate the manner of dispute. In this study, we reviewed the judiciary decrees of litigation regarding for rt-PA usage in Taiwan.

METHODS

In order to reduce the litigation of rt-PA usage in ischemic stroke in Taiwan, a review of the judiciary decrees was conducted. This study was not sponsored by any fund, enterprise, group, person, manufacturer or agency of rt-PA.

In regard to the litigation of rt-PA, related cases in Taiwan were reviewed from the open access database of the Judicial Yuan, Taiwan (<http://jirs.judicial.gov.tw/Index.htm>). The key word was “*血栓溶解劑*” (traditional Chinese) searched in the database which was established and collected the judiciary decrees from the District, High, Supreme, and Administrative Court since 1995. The final date of database search was September 20, 2010. The background, legal dispute and judgment of each case were analyzed.

Medical malpractice is the core of claim in litigation, and is evaluated by if any medical procedure is deviated from the standard of care. If rt-PA treatment is the standard of care, a loss of chance means that patient does not obtain this treatment due to any substandard of care, such as misdiagnosis or delayed diagnosis. A loss of chance responsible by physician is one kind of medical malpractice.

RESULTS

After a detailed survey, there were 6 cases found in the database⁽¹¹⁻¹⁶⁾. All 6 litigations occurred after 2003, one year after rt-PA approval in Taiwan. The background, legal dispute, and judgment were analyzed in each case. Our viewpoint was summarized at the end of each case description.

Part I: Cases Description

1. 96 Med App-1 (High Court Branch at TaiChung, January 30, 2008)

(1) Background

An elderly woman, who had had hypertension, diabetes mellitus and chronic ischemic heart disease, received spinal surgery for lumbar spondylolithiasis on

one morning. Generalized anesthesia was done. After operation, she regained her consciousness and talked clearly. However, she became irritable, conscious change and hemiparesis at that evening. Cranial computerized tomography (CCT) did not show remarkable finding at initial but brainstem infarction 2 days later. Head magnetic resonance imaging (MRI) revealed brainstem infarction with basilar artery occlusion 4 days after index event. Her condition deteriorated later and she expired finally.

(2) Claims

Family plaintiff sued malpractice including inappropriate method of anesthesia, a failure of blood pressure control during operation, a delay of ischemic stroke diagnosis, and a failure of administration of thrombolysis or other appropriate treatment after ischemic stroke. Medical malpractice caused a damage of patient.

Defendants responded that generalized anesthesia was not an inappropriate method of anesthesia in this situation, no overshooting of blood pressure was recorded during operation, ischemic stroke was diagnosed within 4 hours after index event, and rt-PA was contraindicated in postoperative patient, and other vasoactive drugs had been administrated for treatment without delay. Defendants claimed no malpractice, and therefore no duty to the damage of patient.

(3) Court Order

After a review of the available evidence and experts' documents, court concluded that there was no evidence of a deviation of the standard of care or a breach of duty of care in defendants. Action was denied.

(4) Summary of Viewpoint

Thrombolysis was contraindicated as patient received major operation within 12 hours before index event. However, the total interval of a diagnosis of ischemic stroke was recorded as nearly 4 hours by non-neurologist. This time interval did not allege negligence herein but might be considered a deviation of standard of care if patient did not have condition fulfilling the exclusive criteria of rt-PA administration.

2. 95 Med-11 (Taipei District Court, January 21, 2008)

(1) Background

A 74-year-old woman who had had hypertension, old cerebral infarctions, and dementia, suffered right facial weakness, dysarthria, and left hemiparesis on one evening. She arrived the emergent service 40 minutes after attack. Duty doctor revealed a clear consciousness, left central facial weakness and reversible left hemiparesis. NIHSS was 6. CCT showed a right pontine infarction on next morning, 17 hours after index event. Conservative treatment was performed. Hyperglycemia occurred during hospitalization. Unfortunately, a rapid deterioration of consciousness and tetraparesis occurred 2 days later in ward. She was sent to a tertiary medical center no sooner and basilar artery occlusion was found. However, patient expired one more month later due to bacterial sepsis with disseminated intravascular coagulation, acute myocardial infarction, and pontine and medullary infarctions. Basilar artery occlusion was affirmed.

(2) Claims

Family plaintiff sued malpractice including a delay of a diagnosis of ischemic stroke and neuroimaging that made patient to lose the chance of rt-PA and other's treatment, inappropriate fluid supply, and a delay of emergent management upon conscious change. Medical malpractice caused a damage of patient.

Defendants responded that there was an improvement of neurological deficits upon presentation, there was no evidence to arrange CCT in urgency, and a progression of neurological deterioration was related to ongoing basilar artery occlusion, which was refractory to treatment. Defendants claimed no malpractice, and therefore no duty to the damage of patient.

(3) Court Order

After a review of available evidence and experts' documents, court concluded that there was a deviation of the standard of care. The clinical history and neurological examination supported a high possibility of stroke in this patient. However, CCT was obviously delayed in this patient and therefore, patient lost a chance to receive rt-PA to prevent ongoing basilar artery occlusion. The proximate cause of death was brainstem infarction. There was a causal relation between this deviation of

Table 1. The summary of claims, judgment, and patient's outcome in 6 cases of medical litigations due to rt-PA and ischemic stroke

Cases	Claims	Judgment	Patient's outcome
96 Med App-1, 2008 High Court	A loss of chance due to a delay of diagnosis	Contraindication due to recent major operation	Expired
95 Med-11, 2008 Civil Court	A loss of chance due to a delay of diagnosis	Deviant of standard of care	Expired
96 Med-1, ¹ 2007 Civil Court	A failure of administration	Contraindication due to large area of infarctions	Expired
96 Med-2, ¹ 2008 Civil Court	A failure of administration	Contraindication due to previous ischemic stroke within 3 months	Vegetation
94 Med-8, 2006 Civil Court	A loss of chance due to a delay of diagnosis	No evidence of weakness on initial visit	Handicapped
93 Med App-1, ¹ 2004 High Court	A loss of chance due to a delay of diagnosis	Contraindication due to recent major operation	Vegetation

¹ 96 Med-1, 96 Med-2, 93 Med App-1: plaintiff sued defendant criminal negligence but prosecutor did not bring indictment after investigation

standard of care and fatal brainstem infarction. Therefore, there was a breach of duty of care in defendants who did have responsibility for damage of patient. Action was affirmed.

(4) Summary of Viewpoint

A delayed study of CCT is, indeed, a deviation of current standard of care for stroke. However, the dilemma is actually the time to administrate the rt-PA in an individual who shows a progressive improvement of neurological function but the NIHSS is still ≥ 6 . There is no such informatics in clinical guidelines.

3. 96 Med-1 (Banciao District Court, February 26, 2007)

(1) Background

An elderly woman, who had had diabetes mellitus without any treatment before, suffered fluctuation of blood sugar and femoral bone fracture. Urine ketone body level was 5 mg/dl. Physician monitored sugar regularly and started to use insulin to control three days later. Because of fever and pyuria, first-line antibiotics were also introduced. As pain was severe, controlled analgesic containing morphine and fentanyl was given. However,

her consciousness rapidly deteriorated, and pneumonia, sepsis and tetraplegia ensued. CCT showed discrete, multiple infarctions at the bilateral frontal lobes and right basal ganglion. She expired due to pneumonia, sepsis, and respiratory failure no sooner.

(2) Claims

Family plaintiff sued malpractice including a delay of blood sugar control, an early introduction of antibiotics without clinical evidence of infection, an overdose of anesthetics to cause respiratory suppression, a delay of changing antibiotics when sputum was found yellowish, and a failure of rt-PA administration when CCT showed acute infarction. Medical malpractice caused a damage of patient.

Defendants responded that the blood sugar was closely monitored in order to confirm actual blood sugar level and prepare appropriate dose of insulin, an early introduction of first-line antibiotics was due to mild fever and pyuria, there was no overdose of anesthetics that did not cause respiratory suppression, and a detailed survey of infectious source had been done when fever persisted. The rt-PA was not offered due to large area of multiple infarctions. Defendants claimed no malpractice,

and therefore no duty to the damage of patient.

(3) Court Order

After a review of available evidence and experts' documents, duty prosecutor did not find criminal action and denied action of plaintiff. However, plaintiff sued doctor for a breach of duty in Civil Court. Court concluded that there was no breach of duty, and therefore defendants did not have responsibility for a damage of patient. Action was denied.

(4) Summary of Viewpoint

In this case, there is no delay of ischemic stroke diagnosis. Large area of discrete, multiple infarctions is one of the exclusive criteria for rt-PA treatment for acute ischemic stroke. The procedures were under the standard of care.

4. 96 Med-2 (Tainan District Court, June 18, 2008)

(1) Background

A 62-year-old man, who had had diabetes mellitus before, suffered right hemiparesis. Stroke was diagnosed. Patient was discharged 4 days later and suggested to receive physical therapy. The blood sugar level was around 200 mg/dl. Besides of stroke prophylaxis, antidiabetic drugs were prescribed. He suffered severe vertigo and vomiting acutely four days later after discharge. On admission, blood sugar level was 224 mg/dl and antidiabetic drugs were still continued. There was no sugar monitor. He then began to receive physical therapy for weakness. However, recurrence of vomiting occurred 7 days after his second admission. He exhibited difficulty for speaking and swallowing than in prior, and showed asthenia. Aphasia and conscious loss also ensued 2 days later. The blood sugar level was 468 mg/dl. He was resuscitated successfully but became vegetation.

(2) Claims

Family plaintiff sued malpractice including a failure of blood sugar monitor during hospitalization, a recurrence of stroke due to an overshooting of blood sugar, and a failure of efficient treatment, like rt-PA administration, when stroke was diagnosed lastly. Medical malpractice caused a damage of patient.

Defendants responded that blood sugar was similar to the pre-hospital level after admission and antidiabetic

drugs had not been discontinued, a monitor of daily blood sugar daily did not prevent or predict stroke occurrence, there was no causal relation between overshooting of blood sugar and stroke occurrence and even acute stroke could raise blood sugar, and a recurrence of ischemic stroke within 3 months was an exclusive criteria of rt-PA treatment. Defendants claimed no malpractice, and therefore no duty to the damage of patient.

(3) Court Order

After a review of available evidence and experts' documents, duty prosecutor did not find criminal action and denied the action of plaintiff. However, plaintiff sued physician for a breach of duty in Civil Court. Court concluded that there was no breach of duty, and therefore defendants did not have responsibility for damage of patient. Action was denied.

(4) Summary of Viewpoint

In this case, a frequent recurrence of ischemic stroke within 3 months is a contraindication of rt-PA treatment. In regard to law, defendant does not show a breach of duty that is the proximate cause of patient's damage. A 2-day interval between bulbar weakness onset and full-blown symptom of ischemic stroke may increase the risk of misdiagnosis in similar situation.

5. 94 Med-8 (Kaohsiung District Court, December 1, 2006)

(1) Background

A middle-aged woman, who had had hypertension before, was brought by her daughter to primary care clinic because of left upper limb weakness. During interview, she could elevate her upper limbs freely and physician did not find weakness. Mild elevation of blood pressure was noted. She was prescribed anticough medication due to cough and sorethroat. At that night, she found her left limbs weakness during rising up from bed to restroom. She called her family 4 hours later and was sent to local hospital. Ischemic stroke was diagnosed. The rt-PA was not prescribed due to an overtime of therapeutic window. Residual left hemiplegia ensued without improvement.

(2) Claims

Family plaintiff sued malpractice of primary care

physician including a delay of stroke diagnosis that prevented patient to have a chance of appropriate treatment, like rt-PA administration. Medical malpractice caused a damage of patient.

Defendants responded that patient did not show limb weakness on presentation. Defendants claimed no malpractice, and therefore no duty to the damage of patient.

(3) Court Order

After a review of available evidence and experts' documents, court found that objective limb weakness was found when patient woke up at midnight. There was no evidence to allege an underestimation of limb weakness by primary care physician. Court concluded that there was no breach of duty, and therefore defendants did not have responsibility for damage of patient. Action was denied.

(4) Summary of Viewpoint

In this case, there are three possibilities. Firstly, patient did have reversible left side weakness. Secondly, the weakness was so mild enough difficult for detection. Thirdly, stroke with left side limb really occurred after primary care visit. Nobody knows the truth. Court cannot tell us the fact and truth basing solely on law, but which judges our medical performance. The result is a loss, for plaintiff, for defendant, or for both. This case highlights the medical and legal risk of heralding neurological disability. Nevertheless, rt-PA administration is contraindicated in this patient as the time of onset of weakness is uncertain and also overtime of therapeutic window on presentation at local hospital.

6. 93 Med App-1 (High Court Branch at Tainan, July 13, 2004)

(1) Background

A 77-year-old man, who had had hypertension and cardiac dysrhythmia, received cholecystectomy due to cholelithiasis after medical treatment failure. He became drowsy and caught fever on the same night after operation. Because of irritability, his right upper limb was restricted by belt. After antipyretic and antibiotics treatment, fever decreased on the next day morning. He could express his complaint to and negotiate with surgeon. At noon, he was found drowsy again and left side

weakness. CCT was performed 10 minutes later and showed right hemispheric large infarction. Although his neurological and physical deficit improved after aggressive treatment, he became vegetative.

(2) Claims

Two more years later, family plaintiff sued malpractice including a misdiagnosis of stroke as sepsis, and a failure of rt-PA administration due to a delay of diagnosis of ischemic stroke. Since the infarction was large and obvious, it was presumed to be present at least for several hours. Medical malpractice caused a damage of patient.

Defendants responded that sepsis was present basing on laboratory data, and there was no remarkable neurological deficit on the same day of index event until limb weakness was found. CCT was performed within 10 minutes. The time of infarction was unable to be confirmed. The rt-PA was not offered due to a major operation one day before and large hemispheric infarction. Defendants claimed no malpractice, and therefore no duty to the damage of patient.

(3) Court Order

After a review of available evidence and experts' documents, court concluded that there was no breach of duty, and therefore defendants did not have responsibility for damage of patient. Action was denied.

(4) Summary of Viewpoint

In this case, heralding or atypical neurological deficit is obviously the risk of misdiagnosis. Nevertheless, recent major operation is contraindicated for rt-PA administration in acute ischemic stroke.

Part II. Summary of the judicial decrees

1. Plaintiff argued a delay of ischemic stroke diagnosis in 96 Med-App-1, 95 Med-11, 94 Med-8, and 93 Med App-1. Strictly speaking, a delay of diagnosis (definite diagnosis was made over 3 hours after index stroke) was factually considered in 96 Med-App-1 and 96 Med-2 whereas was uncertain in 94 Med-8 and 93 Med-App-1. Proximate cause of damage was not established as rt-PA was contraindicated in 96 Med-App-1 and 96 Med-2.

2. A failure of rt-PA administration was seen in 2 cases after a diagnosis of ischemic stroke. Deviation of standard of care was affirmed in one case whereas a breach of duty was not established in another case due to a presence of contraindication to rt-PA.
3. There were 3 claimants expired, 2 claimants terminating into vegetation, and 1 claimant resulting with handicapped disability.
4. A presence of contraindication to rt-PA administration was present in 4 cases.

DISCUSSION

Till now, there are totally 6 cases of medicolegal litigation concerning for rt-PA in ischemic stroke recorded in Court System, Taiwan⁽¹¹⁻¹⁶⁾. However, it does not mean that the frequency is negligently low as patient/family may not mention a failure of rt-PA administration in litigations or case is closed after reconciliation, negotiation, or criminal investigation. Nevertheless, these cases provide neurologist and non-neurologist medical professional the viewpoint from court in Taiwan.

The characters of rt-PA treatment for ischemic stroke are rapid diagnosis, exclusion, and administration - a competition of running with time. Because the procedures for diagnosis and exclusion for rt-PA treatment are time consumption in ischemic stroke than acute myocardial infarction or peripheral vascular disease⁽⁵⁻⁶⁾, the time pressure is extremely high for first-line neurologist and particularly for non-neurologist and which increases the risk of misdiagnosis or delayed diagnosis. Indeed, patient/family plaintiff claimed a loss of chance of rt-PA treatment due to a delay of diagnosis of or a failure of rt-PA administration after a diagnosis of index ischemic stroke in all 6 cases.

A rapid and accurate diagnosis depends on an early discovery of neurological deficit, a completeness of appropriate tests and imaging, and an accurate decision basing on the final results of examinations. In this series, 5 patients were in-hospitalized and the time for rt-PA administration is, theoretically, expected to be shorter than the out-hospitalized patient. In fact, only 2 patients were definitely diagnosed ischemic stroke vulnerable for

rt-PA treatment within 3 hours. Although rt-PA was contraindicated in 4 patients finally, the time interval between a discovery of neurological deficit and drug administration in hospitalized patient should have been reasonably shortened.

In this series, all cases were not cared or managed by neurologist before index stroke event occurred, in which 5 at the non-neurological ward and 1 at primary care clinic. In the 5 cases of in-hospital stroke, index ischemic stroke occurred after surgical management (96 Med App-1, 93 Med App-1), after anesthesia (96 Med-1), during hospitalization for recent ischemic stroke event (96 Med-2), and admission for recent ischemic stroke event (95 Med-11). An obscuration of neurological manifestation is another important reason for a delay of diagnosis. The initial presentations of index stroke events in 4 cases were irritable, conscious change, severe vomiting, and/or bulbar dysfunction, which should rapidly be cautioned for neurological involvement. In another 2 cases, the dilemma was a fluctuation of motor function upon presentation, which raised the decision difficulty for rt-PA use. The clinical evaluation making a diagnostic differentiation between an exacerbation of underlying primary disease and a new brain attack is a challenge for neurologist, and is even more difficult and time-consuming for non-neurologist. Our series is similar to previous investigations, that the misdiagnosis and delayed diagnosis are not uncommon among non-neurologists⁽¹⁹⁻²¹⁾.

The concept of standard of care is greatly different between medical practice and judiciary system. For example, an extremely high standard of care⁽¹⁷⁾ or no-fault duty⁽¹⁸⁾ in medical practice is objected by physicians but supported by judges. In order to improve the quality of care for common neurological diseases such as stroke, neurological training is crucial for non-neurologist, and may be considered a compulsory program in the Post Graduate Year Course in Taiwan.

In 94 Med-8, patient/family plaintiff claimed that patient suffered left side weakness on presentation. Court denied the action of plaintiff because patient told physician at local hospital that she found weakness on awakening at midnight and primary care physician

defendant also stated that patient could walk and elevate her arm freely without difficulty on presentation. The scenario in this case is similar to the *Kleinmann v. St. Peter's Hospital*⁽²²⁾. On July 8, 1997, plaintiff George Kleinmann collapsed with left side weakness and was sent to the emergent service. Transient ischemic attack was diagnosed by defendant emergent service physician who prescribed heparin for treatment. Neurological deficits progressed on the following days. Left hemiplegia was residual. Plaintiff claimed that defendant misdiagnosed his acute stroke as transient ischemic attack and that let him lose the chance of rt-PA treatment. Plaintiff's wife offered a page of medical record that contained the neurological status compatible with acute stroke at that moment and that was different from the corresponding page provided by defendant. Experts agreed that rt-PA was indicated if acute ischemic stroke, but not transient ischemic attack, was diagnosed at that time. However, the Supreme Court refused to accept plaintiff's copy of medical record as evidence and denied plaintiff's action as there was no evidence to prove a misdiagnosis of ischemic stroke made by defendant. The decree of 94 Med-8 is believed mainly due to subjective statement from patient⁽¹⁵⁾. In general, court always denied action of defendant physician if the medical record did not contain the crucial note in Taiwan⁽²³⁾.

Plaintiffs in all cases claimed a loss of chance of rt-PA treatment due to a delay of ischemic stroke diagnosis, a failure of rt-PA administration after a diagnosis of ischemic stroke, or both. On the other hand, there is no case alleging complication of rt-PA treatment for a deviation of standard of care. This difference may reflect that patient/family are eagerly looking forward for efficient treatment in stroke. Government and health policy maker should be aware of inappropriate rt-PA usage in poor medical resource area when rt-PA is advertised the only drug for acute stroke treatment.

Medical litigation is not simply a linear equation determined by the availability of rt-PA and medical procedure only. Situational factors also include the global insurance budget, legal standard, physician-patient relationship, quality of indication/contraindication and patient's care, and other external and internal element.

Nevertheless, a rapid and accurate evaluation of the necessity of rt-PA treatment is the fundamental obligation for maintaining the standard of care in ischemic stroke.

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