多施設共同研究1：
rt-PA患者登録研究
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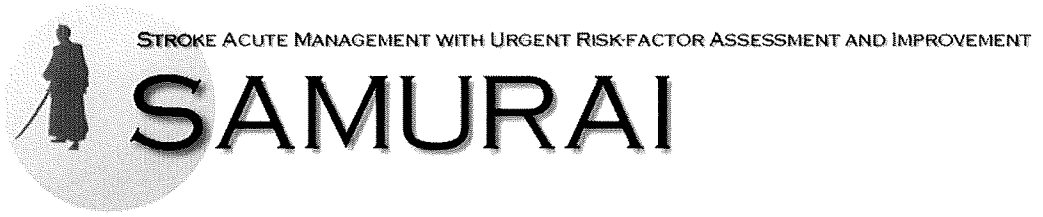
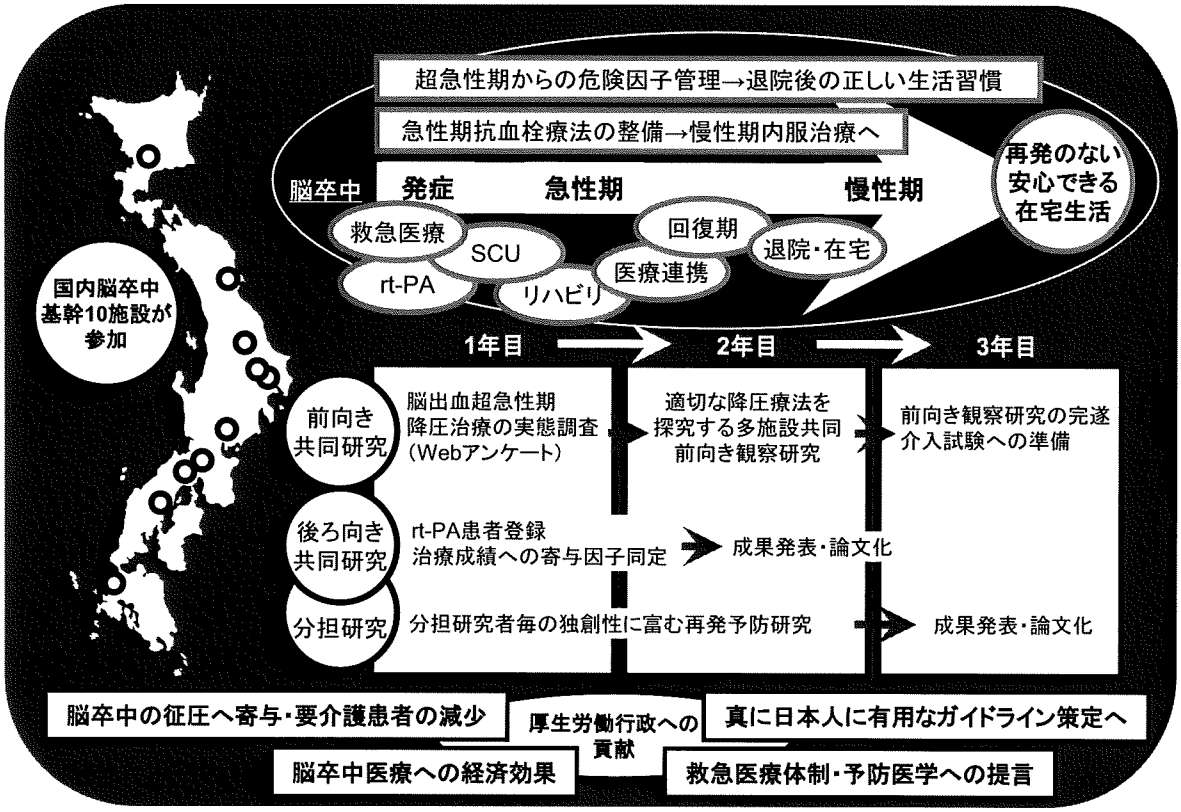


総括研究報告：資料1-a

わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究

本研究班の目的と方針



STROKE ACUTE MANAGEMENT WITH URGENT RISK-FACTOR ASSESSMENT AND IMPROVEMENT

SAMURAI

わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究

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「多施設共同研究 1：rt-PA 患者登録研究」研究主題に関する国内の最新の知見

□はじめに□

脳卒中はしばしば致死的であり、生存例でも家庭復帰や社会復帰が困難なことが多い。脳卒中患者に対して超急性期から慢性期の再発予防に至るまで継ぎ目のない治療の連携が必要であるが、このうちとくに超急性期の治療効果が顕著である。循環器病研究委託費研究 16A-1（主任研究者：岡山　明）の多施設共同前向き登録研究より解明された脳梗塞患者の発症－来院時間と転帰の関係を、表に示す[1]。発症後 24 時間以内に来院した脳梗塞患者を、発症－来院時間で 3 群に分けると、3 時間未満来院群で来院時重症度が高く（NIH Stroke Scale [NIHSS] 高値）、急性期病院退院時の患者自立度が低い（modified Rankin Scale [mRS] 高値、表 1）。しかしながら来院時重症度を含めた背景因子で補正すると、3 時間未満の早期来院群に退院時自立患者が多いことが分かる（表 2）。

表 1

	<3h 574 例	3-8h 632 例	≥8h 611 例	*p*
来院時 NIHSS	9 (4-17)	5(2.3-11)	4 (2 - 7)	<0.001
退院時 mRS	3 (1 - 5)	2 (1 - 4)	2 (1 - 4)	<0.001

表 2

	OR	95% CI	*p*
<3 時間	1.66	1.21 - 2.28	0.002
3 - 8 時間	1.15	0.87 - 1.53	0.325
≥8 時間	1.00	(reference)	-

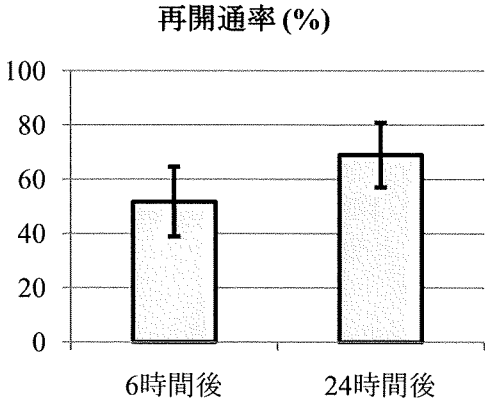
脳梗塞超急性期の治療法として、遺伝子組み換えによる組織型プラスミノゲン・アクティベータ（recombinant tissue-type plasminogen activator, rt-PA）であるアルテプラーゼ（alteplase）の静注療法が知られる。わが国は国外より薬剤用量を低めた治療を承認しているが、その有効性が近年次々と報告されるようになった。本資料では rt-PA 静注療法に関する日本発の知見にこだわって解説する。

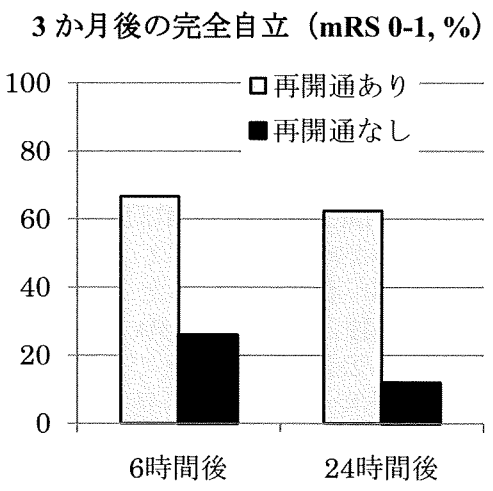
□多施設共同臨床試験□

発症 3 時間以内の脳梗塞患者への rt-PA 静注療法は国際的な標準治療であるが、その承認時期は国内外で差がある。1996 年の米国での承認を皮切りに[2]、2002 年までには欧州や東アジアなどの主要国で承認されたのに対して、わが国では出血性合併症への懸念などの理由で、独自の臨床試験が必要と判断された。2002 年から 2003 年にかけて、第Ⅲ相試験 J-ACT（Japan Alteplase Clinical Trial）[3] が実施され、その成果に基づいて 2005 年 10 月にようやく国内承認された。海外で共通の投与量であるアルテプラーゼ 0.9mg/kg に対して、J-ACT では同薬 0.6mg/kg を用いて試験を行った。用量設定根拠に、急性心筋梗塞における同薬の用量の国内外での違いや、1990 年代初頭の国内臨床試験における rt-PA（デュテプラーゼ）投与量が挙げられる[4]。この試験での有効性と安全性が海外での試験と同等であったため、承認に際しても低用量治療が用いられることになった。

承認条件の一つとして、製造販売後臨床試験の実施が規制当局から求められた。このような経緯で第Ⅳ相試験 J-ACT II が実施された[5]。MR angiography (MRA) で中大脳動脈主幹部ないし分枝の閉塞を認めた脳梗塞患者 58 例を対象に、rt-PA 静注療法後の閉塞動脈の再開通所見と転帰との関係が調べられた。発症 6 時間後の MRA で中大脳動脈の完全ないし部分再開通患者は 51.7%、24 時間後で 69.0%

を占め、再開通患者で 3 か月後に完全自立に復する患者（modified Rankin Scale [mRS] 0-1 に相当）が有意に多かった。





初期重症度や CT での早期虚血所見などを含めた背景要因で補正した後も、6 時間後の再開通所見（オッズ比 6.030、95% CI 1.730 – 21.011）、24 時間後の再開通所見（21.231、3.318 – 135.859）、6 時間後には閉塞していたが 24 時間後に遅れて再開通した所見（15.949、1.710 – 148.762）のいずれも、3 か月後の完全自立に独立して有意に関係した。MRA 上の再開通が転帰に大きく影響することを示した点で、意義深い。

□多施設共同観察研究□

国内承認時のもう一つの承認条件として、承認後 2 年間の使用成績調査（全例調査）が求められた。2 年間で 942 施設から 7492 例が登録され、36 時間以内の症候性頭蓋内出血を 3.5%（95% CI 3.0 – 3.9）に、3 か月以内の死亡を 13.1%（12.4 – 13.9）に、3 か月後の完全自立（mRS 0-1）を 33.1%（31.8 – 34.4）に認めた[6]。欧州での投与推奨基準に合わせた年齢 18～80 歳、NIH Stroke Scale 25 未満の例に限ると、39.0%（37.4 – 40.6）が完全自立しており、欧州での大規模市販後調査 SITS-MOST（Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy）と同等の成績であった[7]。

本厚生労働科学研究班が行った SAMURAI（Stroke Acute Management with Urgent Risk-factor Assessment and Improvement） rt-PA Registry では、国内 10 施設からの rt-PA 静注療法を受けた 600 例（男性 377 例、72±12 歳、治療前 NIH Stroke Scale 中央値 13）を登録し、その治療成績を調べた[8]。36 時間以内の症候性頭蓋内出血（NIH Stroke Scale 1 点以上の増悪）を 3.8%（95% CI 2.6 – 5.7）に、3 か月以内の死亡を 7.2%（5.4 – 9.5）に、3 か月後の完全自立（mRS 0-1）を 33.2%（29.5 – 37.0）に認め、欧州基準に合わせて患者を限ると 40.6%（35.9 – 45.5）が完全自立した。背景要因で補正した後に、若齢、初期軽症、内頸動脈閉塞を伴わないこと、早期虚血所見軽度、治療前に降圧を要しないことの 5 項目が 3 か月後の完全自立に関連し、心不全と入院時血糖高値が死亡に関連した。この登録患者における各種危険因子や画像所見と転帰の関係を、分担研究者の多くが解析し、報告している。Nezu ら[9]は MRI 拡散強調画像での早期虚血変化を ASPECTS (Alberta Stroke Program Early CT Score、10 点満点、低得点ほど虚血が広範)を用いて定量化し、この尺度で 7 点以上が 3 か月後の機能的自立（mRS 0-2）に（オッズ比 1.85、95% CI 1.07 – 3.24）、4 点以下が死亡に関連することを示した（3.61、1.23 – 9.91）。牧原ら[10]は発症前ないし急性期のスタチン服用が転帰に関連しないことを報告した。

わが国の Stroke Unit の有効性を検討する多施設共同前向き研究（SUMO [Stroke Unit Multicenter Observational]研究、主任研究者：峰松一夫）[11]では、承認直前の 10 か月と直後の 3 か月での脳卒中救急診療体制の変化を、国内 84 施設（脳卒中専門病棟を持つ 24 施設を含む）、4620 例を対象に調べた。承認前にも脳梗塞患者の 0.7%に rt-PA 静注が行われていたが、承認後 2.6%に急増した。とくに専門病棟を持つ施設では、0.9%から 5.1%にまで増えた。脳梗塞発症 24 時間以内に拡散強調画像や MRA、頸動脈エコー検査、PT-INR や APTT などの凝血学的検査を行う割合も、承認後に増えた。tPA 静注療法を試行可能な診療体制を、多くの施設が短時間で構築しようと努めたことを、反映している。

□単一施設での臨床研究□

主任研究者らの施設（国立循環器病研究センター）で治療前に MRI, MRA の評価を行った連続 78 例の検討では、NIH Stroke Scale の中央値が投与直前の 12 点から 3 週間後に 3 点まで改善し、5%に症候性頭蓋内出血を認め、3 か月後に 46%が完全自立に至り 3%が死亡した[12]。MRI での ASPECTS 6 点以下と MRA での内頸動脈閉塞所見が、完全自立に至らない患者に独立して有意に関連した。

わが国では MRI の普及率が高く、脳梗塞急性期診療に用いられる機会が多いため、他にも MRI や MRA を評価手段に用いた臨床研究が多い。とくに川崎医科大学（木村和美教授）から、rt-PA 静注療法に関して多くの新知見が発表されている。たとえば拡散強調画像での ASPECTS 5 点以下が、治療 7 日後の NIH Stroke Scale で 20 点以上の予後不良に独立して関連した[13]。中大脳動脈のフィブリン血栓を示すと考えられる T2* 強調画像での susceptibility vessel sign が同定される患者は、閉塞動脈の早期再開通や症状の顕著な改善を認め難かった[14]。またコントラスト経頭蓋ドプラの所見から右左短絡が陽性と考えられる患者は、症状の顕著な改善を認めることが多く、奇異性塞栓症患者が rt-PA 静注療法の良い適応であることが示唆された[15]。徳島大学の Harada ら[16]は、rt-PA 静注療法後に 3 テスラ MRI の T2*強調画像で認められる頭蓋内出血の頻度が 58%と高率であるが、このうち PH 型（塊状出血）を示す例には症状改善を認めることがなく、HI 型（非塊状）を示す例には症状改善や閉塞動脈の再開通が多いことを報告した。

□おわりに□

rt-PA 静注療法の国内承認の契機となった J-ACT、および 2005 年の承認後のおもだった臨床研究を紹介した。この他にカテーテル操作を用いた薬物療法である局所線溶療法として、発症 6 時間以内の中大脳動脈閉塞症例に対するウロキナーゼ局所動注の多施設共同の臨床試験、MELT-Japan （MCA Embolism Local Fibrinolytic Intervention Trial）[17]が実施され、治療群が対照群に比べて 3 か月後の完全自立例が有意に多かった。

わが国独自の低用量 rt-PA 静注療法の効果が多く公表されたことで、同治療の適正用量を考え直す動きも見られ始めた。一方で ECASS-3 （European Cooperative Acute Stroke Study-3）試験の成功に基づいて[18]、欧米では 2009 年に治療可能時間を従来の発症後 3 時間以内から 4.5 時間以内に延ばすことが容認されたが、国内では 3 時間以内という制約が改定されておらず、今後の大きな検討事項の一つである。

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わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
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「多施設共同研究 1：rt-PA 患者登録研究」
rt-PA 患者登録研究の研究計画書

課題名　「t-PA 静注療法を行った脳梗塞患者への急性期危険因子管理・抗血栓療法の実態と治療成績に関する多施設共同研究」

1）研究協力の任意性及び撤回の自由

この研究への参加は自由意思で決められる。本研究への参加を強制するものではなく、不利益になることはない。また一旦参加した場合でも、不利益を受けることなく、いつでも参加を撤回することができ、登録データなどの情報は廃棄され、それ以後は研究目的に用いられることはない。ただし、参加を取り消したときすでに研究結果が論文などで公表されていた場合などのように、登録データなどを廃棄することが出来ない場合がある。

2）研究の目的

2005年10月に急性期脳梗塞症例に対して組織プラスミノゲン・アクティベータ（t-PA、一般名アルテプラーゼ）静注（IV-tPA）療法が適応拡大され、2008年6月現在までに1万症例以上へ使用されていると推定される。IV-tPA療法時には、適正使用指針で血圧高値時の対処や治療開始後24時間以内の抗血栓薬投与の禁止が示されているが、血圧、脈拍、体温や血糖値などのコントロール目標や方法、脳保護薬などの併用薬使用、24時間以降の抗血栓薬使用に関する指針はない。我々は、厚生労働科学研究費補助金による「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」班（主任研究者：豊田一則）を組織し、超急性期脳血管障害の生理学的・血液学的諸量とその管理の実態や急性期抗血栓療法が、長期予後・再発に及ぼす効果を検証し、脳卒中予後判定に有用な危険因子を同定するとともに、日本人に適切な急性期危険因子管理や抗血栓療法による再発予防戦略を構築している。この研究の中で、IV-tPA療法を受けた症例の急性期危険因子管理や、後療法としての急性期抗血栓療法の実態と、予後・頭蓋内出血合併症との関連を後ろ向きに多施設で調査し、同療法時の適切な血圧、脈拍、各種合併症などの管理方法や、後続療法を明らかにする。

3）研究責任者及び研究組織

研究責任者	内科脳血管部門　医長	豊田一則	
研究者	内科脳血管部門　医師	古賀政利	
	内科脳血管部門　医師	永沼基雅	（以下　略）

4）研究の対象及び方法

「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」班の班員が所属する、国立循環器病センター、自治医科大学附属病院、中村記念病院、広南病院、杏林大学附属病院、聖マリアンナ医科大学附属病院、国立病院機構名古屋医療センター、神戸市立医療センター中央市民病院、川崎大学附属病院、国立病院機構九州医療センターで、2005年10月から2008年7月にIV-tPA療法を受けた症例を対象とする。方法は、本研究班の中央事務局（国立循環器病センター内科脳血管内科）が各研究班員の意見を集約して決定したデータベースワークシートを電子媒体で各班員に配布する。各研究班員は、所属施設の対象症例のデータを登録後に2008年11月までに中央事務局に返却する。登録するデータは、個人情報を特定できないものとする。調査項目の詳細を、別紙2に示す。このデータベースをもとに、良好な転帰（退院時／3ヵ月後のmodified

Rankin scale 0もしくは1）や症候性頭蓋内出血に関係する、血液検査データ、バイタルサイン、合併症、画像所見や併用薬剤などを解析し、本邦での適切なIV-tPA療法時の急性期内科的管理と後療法を検討する。

※註：データベースワークシートは、平成20年度報告書に資料2-bとして掲載

5）問題発生時の対応

問題発生時は必ず本研究班の中央事務局（国立循環器病センター内科脳血管部門　古賀政利）に連絡し、適切な対応を検討する。また、必要に応じて各班員と班員が所属する施設の倫理委員会に報告する。

6）研究期間

実施場所は、国立循環器病センター内科脳血管部門とする。実施期間は、倫理委員会による承認を受けた日から2009年3月までとする。

7）研究計画等の開示

研究対象者の希望に応じて、本書面のコピーを開示する。

8）予測される危険性

方法に記した登録データが流出する危険があるが、厳重に管理され持ち出しはできず、また解析は無名化して行うため、ほとんどおこりえない。

9）被験者の利益及び不利益

後ろ向き研究であり、研究対象者に行なわれる治療は通常の診療で一般的に行なわれているものであるので、通常の診療を上回る利益、不利益はない。

10）費用負担に関する事項

本研究に関する経費は、厚生労働科学研究費補助金による「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」班（研究課題番号H20 -循環器等（生習）一般-019、主任研究者：豊田一則）の研究費より支出する。研究対象者に対する謝金、交通費等の支払いは行われない。

11）知的所有権に関する事項

知的所有権が発生した場合、その権利は国・研究機関・研究遂行者などに属し、研究対象者に帰属することはない。

12）倫理的配慮

12-1）医学研究及び医療行為の対象となる個人の人権の擁護

研究対象者の人権の擁護のために、データを登録する前に研究の内容、目的および方法を含めて各施設の掲示板などに掲示する。また、得られたいかなる個人情報について秘密が厳守されることを保証する。

12-2）医学研究及び医療行為の対象となる個人への利益と不利益

利益：後ろ向き研究であり、研究対象者に行なわれる治療は通常の診療で一般的に行なわれているものであるので、通常の診療を上回る利益はない。今後IV-tPA療法を受ける脳梗塞患者にとってより適切なIV-tPA療法時の対応を確立できる可能性がある。

不利益：後ろ向き研究であり、研究対象者に行なわれる治療は通常の診療で一般的に行なわれているものであるので、通常の診療を上回る不利益はない。ただし、個人情報の流出は不利益となるため、以下の方針で臨む。すなわち、本研究は後ろ向きに多施設

の研究対象者データをまとめて解析するものであり、各対象者個人を特定できるような検討は行わない。各施設のデータを収集する時点で、研究用の登録番号による管理とし、各施設のデータとの照合が出来ないように管理する。しかしながら、問題発生時には適切な対応を行う。登録データの研究目的使用に当たっては研究責任者によりデータ管理を徹底し、学会・論文などの研究成果発表以外の部外へ個人プライバシーに関わるデータが流出しないよう注意する。また個人情報の流出により個人のプライバシーを侵害した可能性が生じた場合はすぐに倫理委員会に報告する。

12-3) 医学的貢献度

IV-tPA療法は、有効性が高い一方で出血性合併症の危険性もある。いかに、安全性を確保しながら有効性を高める治療を確立するかが重要である。本研究の解析結果によりIV-tPA療法時の、より適切な対象者選択、適切な血圧管理、後療法の選択などの治療管理戦略を構築できる可能性がある。

12-4) 医学研究及び医療行為の対象となる個人に理解を求め同意を得る方法

データを登録する前に、研究の内容、目的および方法を含めて班員の所属する施設の掲示板などに掲示する。研究対象者またはその家族等から研究への不参加の申し出があれば、そのデータは破棄し、それ以外の研究対象者のデータを用いて研究を行う。ただし、申し出があったときすでに研究結果が論文などで公表されていた場合などのように、調査結果などを廃棄することが出来ない場合がある。登録データは研究者により厳重に保護されること、臨床成績を医学雑誌などに発表する際には最大限にプライバシー保護に努め、研究対象者の名前や身元などを明らかにするようなことはない。なお、この研究は一般保険診療の枠外で行われるため、患者から診療録閲覧の請求を受けた場合はその対象とならない。

本研究は以下の 4 点を満たすため、2007 年 8 月 16 日に改正された文部科学省・厚生労働省の疫学研究倫理指針に従い、研究内容等を施設内の掲示板に掲示・広報することで研究対象者に通知する。すなわち、(1)研究対象者に対して最小限の危険を超える危険を含まず、(2)研究内容を掲示板に掲示して広報することが研究対象者の不利益とならず、(3)各対象者から同意書を取得する方法では重症例・死亡例の登録に概して同意を得がたく、研究結果に大きな歪みを来たす危険が高く、(4)本研究の社会的な重要性が高い。

13) 行政機関個人情報保護法に基づく追記事項

13-1) 各班員の所属する施設で方法に記す研究対象者のデータを CD-R や USB メモリに登録する。

13-2) データの管理は解析用 PC1 台で行い、件数は最大 1000 例とする。

13-3) データの保存媒体の安全管理方法

アクセス制御と使用者認証によりシステムは管理し、専用のＰＣ端末の部屋には施錠による盗難防止

13-4) 匿名化の方法およびそのタイミング

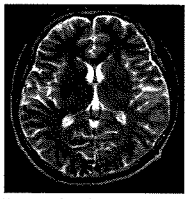
匿名化は各班員の所属する施設からデータを登録する時点で行う。解析ソフトは患者名等個人情報を取得しない

13-5) 臨床情報も同じく匿名化し、豊田一則ないし古賀政利が管理する。

13-6) 利用目的を変更された場合は、再び掲示板などに公示する。

厚生労働科学研究による「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」より
『t-PA静注療法を行った脳梗塞患者への急性期危険因子管理・抗血栓療法の実態と治療成績に関する多施設共同研究』

患者さんへのお知らせ



わが国において脳卒中は死因の第 3 位、要介護性疾患の第 1 位を占め、国民の高齢化とともに、さらに患者数が増えています。とくに脳梗塞は脳卒中の約 7 割を占め、その治療法の確立が急がれます。2005 年 10 月から脳梗塞の急性期治療薬として、脳梗塞の原因となる脳動脈内の血栓を溶かす組織プラスミノゲン・アクティベータ（t-PA、一般名：アルテプラーゼ）静脈注射薬を使用できるようになり、2008 年 6 月までに全国で 1 万人以上の方へ使用されています。従来の治療薬に比べて効果が優れていますが、今後さらなる治療効果の改善を図る必要があります。

本研究の目的は、現在までにt-PA治療を受けた方がどのくらい良くなったか、この治療の成績に、血圧や血液検査のデータ、治療時もしくはその後に使用したお薬などがどのような影響を与えたかを、国内多施設で協力して検討し、望ましい治療時の管理法とその後の治療法を決めることです。

研究の方法：すべての実施施設で統一された様式を用いて、研究の対象となる方々の名前や住所などの個人情報を削除した上で、脳梗塞の性状や治療内容、治療後の経過をカルテから調べさせていただき、登録します。この研究では、t-PA治療の効果を検証するため、全例の登録が必要となります。治療への介入試験ではなく、特定の試料を採取いたしませんので、個別の同意はいただかないことにいたします。そのため、本研究の目的を含む研究の実施についての情報を公開し、登録の中止を希望される場合にはご連絡をいただくことと致しました。研究の対象となる方々に不利益とならないよう万全の対策をとり、調査記録なども研究目的以外に用いることはありません。個人を特定できる情報をすべて削除した上で登録を行うことで、個人情報を厳重に保護し、研究を実施いたします。

実施施設：国立循環器病センターを中心に全国の 10 か所の病院
対象となる方：2005 年 10 月から 2008 年 7 月までに t-PA 治療を受けた方

ご質問、ご不明の点がありましたら、下記連絡先までご連絡ください。
ご協力、お願い申し上げます。

事務局：
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Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0·6 mg/kg) alteplase therapy for ischaemic stroke

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Aims **To determine the predictors of efficacy, including magnetic resonance imaging information, for low-dose intravenous alteplase therapy for stroke patients.**

Methods **Seventy-eight patients were prospectively enrolled in a single Stroke Unit (SU) receiving alteplase at a dose of 0·6 mg/kg during the initial 27 months after its approval in Japan. Ischaemic changes and vascular lesions were identified using computed tomography, diffusion-weighted magnetic resonance imaging, and magnetic resonance angiography. Early ischaemic signs were assessed using the Alberta Stroke Program Early CT Score.**

Results **The median baseline National Institutes of Health Stroke Scale score of 78 patients was 12. In 19 patients (24%), the National Institutes of Health Stroke Scale score improved by ≥8 points at 24 h. After multivariate adjustment, occlusion at the internal carotid artery (odds ratio 11·82, 95% confidence interval 1·73–142·74), Alberta Stroke Program Early CT Score on diffusion-weighted imaging ≤6 (15·23, 1·88–351·50), and a lower National Institutes of Health Stroke Scale score (1·24, 1·08–1·47, per 1-point decrease) were inversely correlated with early improvement. Four patients (5%) had symptomatic intracranial haemorrhage. At 3 months, 76 patients (98%) survived, and 36 of 78 patients (46%) overall, but only two of 19 patients (11%) with internal carotid artery occlusion, had a favourable functional outcome, corresponding to a modified Rankin scale score ≤1. After multivariate adjustment, internal carotid artery occlusion (odds ratio 15·84, 95% confidence interval 3·12–128·69) and Alberta Stroke Program Early CT Score on diffusion-weighted imaging ≤6 (15·62, 1·78–410·12) were independent predictors of poor outcome.**

Conclusions **Intravenous alteplase therapy at a dose of 0·6 mg/kg resulted in a relatively good overall outcome when compared with outcomes reported by western studies using an alteplase dose of 0·9 mg/kg. However, patients with occlusion at the internal carotid artery did not respond to this low-dose alteplase therapy.**

Key words: carotid artery occlusion, cerebral infarction, stroke outcome, thrombolysis, tissue plasminogen activator

Introduction

Intravenous (i.v.) alteplase therapy at a dose of 0·9 mg/kg has been approved internationally for the treatment of hyperacute ischaemic stroke (1–4). However, a large population study indicated that Asian patients had a 2·3-fold higher risk of in-hospital mortality after thrombolysis compared with Caucasian patients (5). Because Asian ethnic origin is an important risk factor for haemorrhagic stroke (6), a smaller dose of alteplase may be appropriate for Asian stroke patients. After a dose comparison study using duteplase (7) and a multicentre study using a single dose of alteplase [Japan Alteplase Clinical Trial (J-ACT)] (8), i.v. alteplase therapy with a dose of 0·6 mg/kg was approved in Japan in 2005 (9), although there has never been a head-to-head comparison of the alteplase dose of 0·9 vs. 0·6 mg/kg. Immediately after approval, the Japan Stroke Society published the Japanese guidelines for this low-dose

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Conflict of interest: None.

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i.v. alteplase therapy (10), and arranged for educational lectures in every prefecture throughout Japan (11). However, the efficacy of this low-dose therapy in routine clinical practice has not yet been clarified.

Magnetic resonance imaging (MRI)-based thrombolysis up to 6 h after stroke onset might be safer than standard computed tomography (CT)-based thrombolysis (12, 13). To introduce i.v. alteplase therapy into our institute, MRI was considered better for understanding the stroke profile for two reasons: diffusion-weighted imaging (DWI) would allow assessment of the early ischaemic change, and MR angiography (MRA) would allow accurate identification of the site of arterial occlusion. The Alberta Stroke Program Early CT Score (ASPECTS) was a quantitative scoring method of the early ischaemic signs for CT (14, 15), and the scoring of ASPECTS using DWI has been reported to be similarly available with the scoring using CT (16). Sites of arterial occlusion may be critical for the outcome of thrombolysis. Occlusions at the terminal internal carotid artery (ICA) and at the tandem lesion of the ICA and middle cerebral artery (MCA) detected on transcranial Doppler (TCD) have been shown to be predictive of a poor outcome after i.v. alteplase (17, 18). Because Japanese patients do not often have a sufficient cranial window for TCD (19), TCD is not appropriate for routine use in thrombolysis; MRA may be a promising alternative.

The goal of this study was to identify the clinical and radiological (including DWI and MRA) predictors of clinical efficacy for low-dose i.v. alteplase given at a dose of 0·6 mg/kg to stroke patients.

Methods

We prospectively enrolled 333 consecutive patients who were admitted within 3 h after the onset of ischaemic stroke or transient ischaemic attack to the stroke care unit in the National Cardiovascular Center between October 2005 (when i.v. alteplase therapy was approved in Japan) and December 2007. Patient eligibility for alteplase therapy was determined principally based on the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and J-ACT (1, 8). Patients with CT evidence of extensive early ischaemic change (affecting more than one-third of the MCA territory) were excluded from the study in principle according to the J-ACT. Those with the similar DWI evidence were also excluded. The local Ethics Committee approved the research protocol. Either patients or their representatives gave their written informed consent.

Each patient received a single alteplase dose of 0·6 mg/kg (not exceeding 60 mg) intravenously, with 10% given as a bolus, followed by a continuous i.v. infusion of the remainder over 1 h. As in the NINDS study (1), use of antithrombotic agents was prohibited for 24 h after onset, blood pressure was maintained at $<180/105$ mmHg, and neurological symptoms were frequently monitored. Unless contraindicated (as in renal insufficiency), all patients were given a free radical scavenger, edaravone, intravenously in the hyperacute stage (20). The neurological deficits on admission were evaluated using the National Institutes of Health stroke scale (NIHSS) score just before and right after the 1-h alteplase infusion, 1 h later, 24 h later, and 3 weeks later. 'Early improvement' was defined as a decrease in the score ≥ 8 points or the score of 0 at 24 h posttherapy compared with the initial score (21, 22). Activities of daily living (ADL) 3 months poststroke were assessed using the modified Rankin scale (mRS) score. A score ≤ 1 at 3 months poststroke was defined as a 'favourable chronic outcome' and a score ≥ 2 or death was defined as an 'unfavourable chronic outcome'.

Before alteplase therapy, all patients underwent brain non-contrast CT, as well as DWI and intracranial MRA (unless contraindicated). The ASPECTS was calculated on both CT and DWI by 2 or more vascular neurologists (14, 15). The patients were divided into four groups according to the arterial occlusion sites ipsilateral to ischaemia: (1) those with the ICA occlusion; (2) those with the MCA trunk (M1) occlusion; (3) those with the MCA branch (M2) occlusion; and (4) those with occlusion at other sites, including the anterior and posterior cerebral arteries and vertebrobasilar arteries, or those without documented occlusion on MRA. CT scans were repeated 24–36 h posttherapy. Symptomatic intracerebral haemorrhage (ICH) was defined as CT evidence of new ICH within the initial 36 h with neurological deterioration corresponding to an increase of ≥ 4 point from the baseline NIHSS score.

The patients' risk factors included sex, age, hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg before stroke or a history of antihypertensive medication), diabetes mellitus (fasting blood glucose $\geq 7{\cdot}0$ mmol/l, a positive 75 g oral glucose tolerance test, or a history of antidiabetic medication), hypercholesterolaemia (serum total cholesterol $\geq 5{\cdot}7$ mmol/l or a history of antihypercholesterolaemic medication), atrial fibrillation, current smoking habit, current alcohol consumption, a history of ischaemic stroke, and use of antithrombotic agents before stroke. On admission, blood pressure and the blood parameters listed in Table 1 and its footnote were measured. Based on neurological, radiological, cardiological, and haematological profiles, the stroke subtype was determined during hospitalisation by a consensus of vascular neurologists according to the TOAST subtype classification system (23): cardioembolism, large-artery atherosclerosis (atherothrombosis), small-artery arteriosclerosis (lacune), and stroke of other determined or undetermined aetiology.

Statistics

Of the patients who were treated with i.v. alteplase, those with a premorbid mRS score ≥ 2 and those who were contraindicated to MRI were excluded from analyses. Baseline clinical characteristics and stroke features were compared between patients with and without early improvement, and between patients with favourable and unfavourable chronic outcomes, using the

Table 1 Underlying risk factors

		Improvement at 24 h		Outcome at 3 months	
	Total	Improved	Nonimproved	Favourable	Unfavourble
Number	78	19	59	36	42
Age	71±9	71±9	71±9	70±7	72±9
Male	59 (76)	14 (74)	45 (76)	28 (78)	31 (74)
Hypertension	60 (77)	17 (89)	43 (73)	23 (64)	37 (88)*
Diabetes mellitus	16 (21)	3 (16)	13 (22)	9 (21)	7 (19)
Hypercholesterolaemia	31 (40)	6 (32)	25 (42)	15 (42)	16 (38)
Atrial fibrillation	34 (44)	9 (47)	25 (42)	13 (36)	21 (50)
Current smoking	25 (32)	2 (11)	23 (39)*	8 (22)	17 (40)†
Current drinking	36 (46)	9 (47)	27 (46)	18 (50)	18 (43)
Previous ischaemic stroke	13 (17)	3 (16)	10 (17)	7 (17)	6 (17)
Antithrombotic use	30 (38)	10 (53)	20 (34)	17 (47)	13 (31)

Data are mean ± SD for age and number of patients (%) for others. *$P<0.05$. †$P<0.1$ vs. 'improved' or 'favourable'.

χ^2-test, unpaired Student's *t*-test, or Mann–Whitney's *U*-test, as appropriate. To evaluate the correlation between ASPECTS on CT and ASPECTS on DWI, linear regression analysis and the Pearson correlation coefficient were used. Optimal cutoff ASPECTS for predicting early improvement and chronic outcome were determined using receiver operating characteristic (ROC) curves. To identify the independent risk factors related to early improvement and chronic outcome, sex, age, and the baseline variables that were automatically selected in a stepwise selection method were included in the multivariate analysis. A P value <0.05 was considered to be significant and a P value <0.1 was considered to be marginally significant. All calculations were performed using jmp 7 software (SAS Institute Inc., Cary, NC).

Results

Of the 333 patients who visited our SU within 3 h after the onset of ischaemic stroke, 94 (28%) were treated with i.v. alteplase. They accounted for 10% of the 948 inpatients with acute ischaemic stroke in our centre during the same period. Of these 94 patients, five patients with the premorbid mRS score ≥2 and 11 patients who were contraindicated to MRI were excluded, which left 78 patients in the study. The underlying clinical characteristics of the 78 patients are summarised in Table 1, and stroke features and data on admission are summarised in Table 2. The ASPECTS on the admission CT and those on the admission DWI were well correlated ($R^2 = 0.326$, $P<0.001$, Fig. 1).

The overall median NIHSS score declined from 12 at baseline to 9 immediately after the 1-h alteplase infusion, 9 at 1 h later, 7·5 at 24 h, and 3 at 3 weeks. Changes in the median NIHSS score by the different sites of occlusion are plotted in Fig. 2, which shows a plateau in patients with ICA occlusion, and a gradual decrease in the other patients. At 24 h, the NIHSS score of 19 patients (24%) improved by ≥8 points. Cutoff ASPECTS on CT based on ROC curves was ≤7 and cutoff ASPECTS on DWI was ≤6 for early improvement at 24 h. Current smoking ($P = 0.021$) and the initial NIHSS score ($P = 0.030$) were significantly different between patients with and without early improvement (Tables 1 and 2). After adjustment for age, sex, and selected variables using the stepwise selection method, ICA occlusion (odds ratio 11·82, 95% CI 1·73–142·74), ASPECTS on DWI ≤6 (15·23, 1·88–351·50), and a lower NIHSS score (1·24, 1·08–1·47, per 1-point decrease) were inversely correlated with early improvement (Table 3).

Four patients (5%) had symptomatic ICH within the initial 36 h; the initial occlusion site was the ICA in 1 (ASPECTS on DWI: 9), the M1 in 2 (ASPECTS on DWI: 4 for both), and the M2 in another (ASPECTS on DWI: 5). Of these, a patient with the ICA occlusion died in the acute stage, two patients with the M1 occlusion received surgical evacuation for severe brain oedema, and a patient with the M2 occlusion had a 3-month mRS score of 3.

At 3 months, two (2%) patients were dead; both of them had ICA occlusion. Of 78 patients overall, 36 (46%) recovered to a favourable functional outcome at 3 months. However, only two of 19 patients (11%) with ICA occlusion had a favourable outcome (Fig. 3). Cutoff ASPECTS on CT based on ROC curves was ≤9 and cutoff ASPECTS on DWI was ≤6 for chronic outcome. The sites of occlusion were significantly different between patients with favourable outcomes and those with unfavourable outcomes at 3 months ($P = 0.001$, Table 2). Compared with patients with favourable outcomes, those with unfavourable outcomes were more hypertensive ($P = 0.011$), more frequently showed ASPECTS on DWI ≤6 ($P = 0.008$), had higher NIHSS scores ($P = 0.002$), tended to more frequently have a smoking habit ($P = 0.085$), and tended to have higher initial diastolic blood pressures ($P = 0.066$, Tables 1 and 2). After multivariate adjustment, ICA occlusion (odds ratio 15·84, 95% CI 3·12–128·69) and ASPECTS on DWI ≤6 (15·62, 1·78–410·12) were independent predictors of an unfavourable outcome (Table 4).

Table 2 Stroke features and physiological data on admission

		Improvement at 24 h		Outcome at 3 months	
	Total	Improved	Nonimproved	Favourable	Unfavourble
Number	78	19	59	36	42
Onset-to-needle time (min)	136±27	126±33	139±25	134±29	137±26
Subtypes					
Cardioembolic	40 (51)	11 (58)	29 (49)	19 (53)	21 (50)
Atherothrombotic	16 (21)	2 (11)	14 (24)	7 (19)	9 (21)
Lacunar	2 (3)	0	2 (3)	0	2 (5)
Other	20 (26)	6 (31)	14 (24)	10 (28)	10 (24)
Site of occlusion on MRA					
ICA	19 (24)	2 (11)	17 (29)	2 (6)	17 (40)*
M1	20 (26)	7 (37)	13 (22)	9 (25)	11 (26)
M2	12 (15)	4 (21)	8 (14)	9 (25)	3 (7)
Others/no occlusion	27 (35)	6 (32)	21 (36)	16 (44)	11 (26)
Vertebrobasilar infarcts	6 (8)	3 (16)	3 (5)	4 (11)	2 (5)
ASPECTS on CT	9 (8–10)	10 (8–10)	9 (8–10)	10 (8–10)	9 (8–10)
ASPECTS on CT≤7‡	9 (12)	1 (5)	8 (14)	–	–
ASPECTS on CT≤9‡	27 (35)	–	–	9 (25)	18 (43)
ASPECTS on DWI	9 (8–10)	9 (8–10)	9 (7–10)	9 (8–10)	8·5 (7–10)†
ASPECTS on DWI≤6‡	11 (14)	1 (5)	10 (17)	1 (3)	10 (24)*
Initial NIHSS score	12 (8–18)	13 (12–20)	12 (7–18)*	11·5 (7–13)	14·5 (10–20)*
Data on admission					
Systolic blood pressure (mmHg)	161±35	154±39	163±33	155±31	166±37
Diastolic blood pressure (mmHg)	86±19	83±23	87±17	82±19	89±18†
Blood glucose (mmol/l)	7·5±3·0	7·5±2·1	7·5±3·2	7·7±3·1	7·3±2·8

Data are number of patients (%), mean±SD for continuous variables, and median (interquartile range) for discontinuous variables. Among blood tests, white blood cell count, haemoglobin, platelet count, highly sensitive C-reactive protein, total protein, albumin, blood urea nitrogen, creatinine, uric acid, aspartate/alanine aminotransferase, total/direct bilirubin, low/high-density lipoprotein, and triglyceride, as well as glucose were not different ($P>0·1$) between patients with and without improvement at 24 h or between patients with favourable and unfavourable outcome at 3 months. *$P<0·05$. †$P<0·1$ vs. 'improved' or 'favourable'. ‡Cutoff ASPECTS on CT based on ROC curves is ≤7 for early improvement and ≤9 for chronic outcome. Cutoff ASPECTS on DWI is ≤6 for both early improvement and chronic outcome. ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; DWI, diffusion-weighted imaging; ICA, internal carotid artery; MRA, MR angiography; NIHSS, National Institutes of Health Stroke Scale.

Discussion

The present study determined the efficacy and safety of low dose, i.v. alteplase therapy at a dose of 0·6 mg/kg for stroke patients, which is a therapeutic strategy that has only been approved in Japan (10, 11). The first major finding was that 24% of patients receiving therapy showed improvement of the NIHSS score ≥8 points within the initial 24 h, and 46% of the patients recovered completely independent ADL (corresponding to an mRS ≤1) at 3 months, while 5% had symptomatic ICH within the initial 36 h, and 2% were dead at 3 months. The second major finding was that occlusion at the ICA documented on MRA was associated with a several fold increased risk of failure to show early improvement and that of an unfavourable chronic outcome compared with other occlusion locations. This finding indicates an obvious limitation of this low-dose alteplase therapy. The third major finding was that ASPECTS on DWI ≤6 was another independent predictor for failure to show early improvement and an unfavourable chronic outcome.

Major neurological improvement of the NIHSS score ≥8 points is recommended as a useful marker of thrombolytic activity (21, 22). Relatively few patients showed a major improvement in the present study compared with those in the NINDS trial (32%) (22). In contrast, the 3-month outcome in our patients (46% of the patients had an mRS ≤1) was relatively good compared with those reported from western countries using alteplase at a dose of 0·9 mg/kg, including the NINDS trial (39%) (1), SITS-MOST (39%) (4), and the pooled results of the randomised trials (42%) (24). Our institute has extensive experience in stroke thrombolysis, participating in several clinical trials as a core institute (7, 8) and performing i.v. thrombolysis for 10% of acute ischaemic stroke patients. Thus, the present success may be institute specific.

Before the NINDS study (1), several trials reported that ICA occlusion documented on conventional angiogram responds poorly to i.v. thrombolysis (25–27). ICA occlusion or tandem ICA/MCA occlusion has been shown to be resistant to i.v. alteplase at a dose of 0·9 mg/kg, as documented on MRA or CT angiogram (28) and on TCD (17, 18). The present study confirmed these previous results and highlighted the strong influence of ICA occlusion on poor outcome in Japanese patients after i.v. alteplase at a lower dose than other countries, even after adjustment for other known confounders. Although

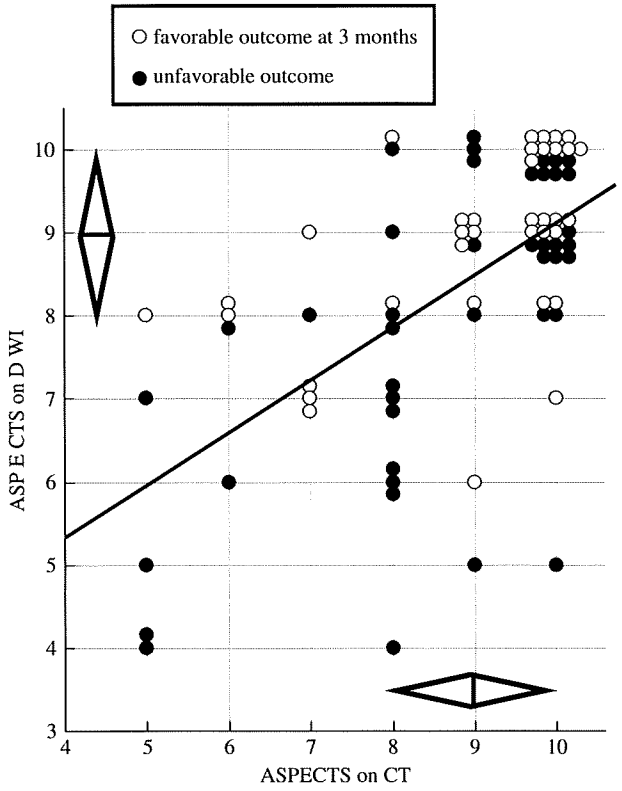

Fig. 1 Correlation between ASPECTS on CT and ASPECTS on diffusion-weighted imaging (DWI) $R^2 = 0{\cdot}326$, $P<0{\cdot}001$. Diamonds show the median value (9) and interquartile range (8–10) of Alberta Stroke Program Early CT Score (ASPECTS) on computed tomography and ASPECTS on DWI.

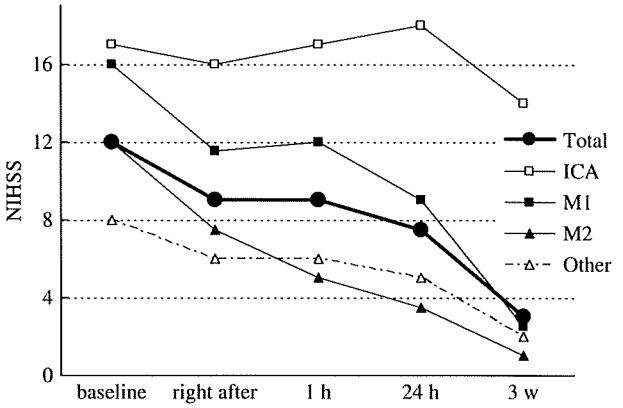

Fig. 2 Changes in the median National Institutes of Health Stroke Scale score by different sites of occlusion.

Table 3 Multivariate-adjusted odds ratios (OR) for failure in early improvement

	OR	95% CI	*P*-value
Age, per 10-year increase	0·94	0·34–2·48	0·901
Male	0·38	0·05–1·99	0·279
Hypertension	0·35	0·05–1·80	0·244
Current smoking	4·83	0·83–42·22	0·104
Antithrombotic use	0·26	0·06–1·09	0·075
ICA occlusion	11·82	1·73–142·74	0·025
ASPECTS on DWI ≤6	15·23	1·88–351·50	0·028
Initial NIHSS score, per 1-point decrease	1·24	1·08–1·47	0·005

Sex, age, and variables that were automatically selected in a stepwise selection method were used for the analysis. ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; DWI, diffusion-weighted imaging; ICA, internal carotid artery.

MRI is expensive and has some potential risks (29), it allows accurate identification of intracranial artery occlusion. In Japan, MRI equipment is widely available; thus, MRI-based thrombolysis appears to be acceptable.

Another advantage of MRI over CT for stroke diagnosis is easier identification of hyperacute ischaemia using DWI (30, 31). A positive relation between ASPECTS assessed on CT and on DWI was established (16). The ASPECTS on DWI ≤ 5 was recently reported to be a predictor for the NIHSS score ≥ 20 at 7 days after i.v. alteplase therapy (32). In the present study, ASPECTS on DWI, but not ASPECTS on CT, was predictive of both early improvement and chronic outcome after multivariate adjustment.

Other than the ICA occlusion and ASPECTS on DWI, a high initial NIHSS score was associated with a major early neurological improvement; this seems to be simply because high baseline points are needed for a marked decrease of ≥ 8 points.

The present study had several limitations. Because this was an observational study from a single SU, our results could not be compared with those from other centres, with those of patients not receiving thrombolysis, and with those of Japanese patients treated with alteplase at a dose of 0·9 mg/kg. Second, the study also lacked data on recanalisation of the occluded artery after alteplase. Third, fewer lacunar patients were included than previous studies on i.v. alteplase therapy (1, 4). Because patients with minor damage corresponding to the NIHSS score ≤ 4 were not treated with alteplase in principle in our institute based on the criteria of J-ACT (8) and more than half the Japanese patients with lacunar stroke were reported to exhibit such minor deficits (33), and because cardioembolic patients generally visit hospitals much earlier than patients with other subtypes (33), the distribution of stroke subtypes appeared to be affected. In general, the efficacy of i.v. alteplase is thought to be similar among different stroke subtypes (1, 34).

In conclusion, i.v. alteplase therapy at 0·6 mg/kg resulted in a relatively good outcome for the present patients, although ICA occlusion and low ASPECTS on DWI were strong predictors of a poor outcome. For patients having ICA occlusion, alternatives may be required, including higher dose alteplase, combined i.v./intraarterial thrombolysis, or possibly mechanical thrombectomy using a thrombus-removal device (35). A randomised, multicentre trial (the Interventional Management of Stroke III Trial) is ongoing to determine the efficacy of the combined i.v./intraarterial

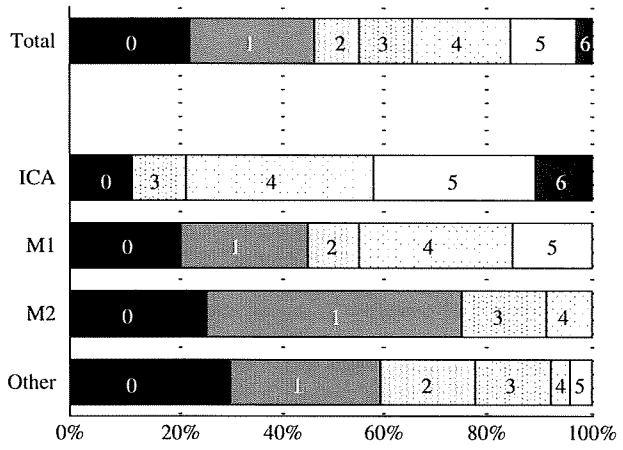

Fig. 3 Modified Rankin scale score at 3 months by different sites of occlusion.

Table 4 Multivariate-adjusted odds ratios (OR) for unfavorable chronic outcome

	OR	95% CI	*P*-value
Age, per 10-year increase	0·96	0·44–2·06	0·911
Male	0·59	0·12–2·73	0·496
Hypertension	3·99	1·02–18·56	0·058
Atrial fibrillation	2·41	0·69–9·17	0·175
Current smoking	4·03	0·98–19·27	0·063
Antithrombotic use	0·29	0·07–1·09	0·078
ICA occlusion	15·84	3·12–128·69	0·003
ASPECTS on DWI≤6	15·62	1·78–410·12	0·034

Sex, age, and variables that were automatically selected in a stepwise selection method were used for the analysis. ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; DWI, diffusion-weighted imaging; ICA, internal carotid artery.

approach to recanalisation using the thrombus-removal device, infusion of alteplase with low-energy ultrasound at the site of the thrombus, or infusion of alteplase via a standard microcatheter (36).

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Routine Use of Intravenous Low-Dose Recombinant Tissue Plasminogen Activator in Japanese Patients: General Outcomes and Prognostic Factors From the SAMURAI Register

Kazunori Toyoda, Masatoshi Koga, Masaki Naganuma, Yoshiaki Shiokawa, Jyoji Nakagawara, Eisuke Furui, Kazumi Kimura, Hiroshi Yamagami, Yasushi Okada, Yasuhiro Hasegawa, Kazuomi Kario, Satoshi Okuda, Kazutoshi Nishiyama, Kazuo Minematsu and for the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators

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Routine Use of Intravenous Low-Dose Recombinant Tissue Plasminogen Activator in Japanese Patients

General Outcomes and Prognostic Factors From the SAMURAI Register

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for the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators

Background and Purpose—A retrospective, multicenter, observational study was conducted to document clinical outcomes and to identify outcome predictors in patients treated with low-dose intravenous recombinant tissue plasminogen activator (0.6 mg/kg alteplase), which was approved in Japan in 2005, within 3 hours of stroke onset.

Methods—Consecutive patients with stroke treated with recombinant tissue plasminogen activator in 10 Japanese stroke centers were included.

Results—A total of 600 patients (377 men, 72±12 years old) were studied. Median National Institutes of Health Stroke Scale scores decreased from 13 before recombinant tissue plasminogen activator to 8 at 24 hours later. Symptomatic intracerebral hemorrhage within 36 hours with a ≥1-point increase from the baseline National Institutes of Health Stroke Scale score developed in 23 patients (3.8%; 95% CI, 2.6% to 5.7%). At 3 months, 43 patients had died (7.2%; 5.4% to 9.5%), and 199 patients (33.2%; 29.5% to 37.0%) had a modified Rankin Scale score ≤1. Analysis of 399 patients with a premorbid modified Rankin Scale score ≤1 who met the criteria of the European license (≤80 years old, an initial National Institutes of Health Stroke Scale score ≤24, etc) showed that 40.6% (35.9% to 45.5%) had a 3-month modified Rankin Scale score ≤1. After multivariate adjustment, younger age, lower initial National Institutes of Health Stroke Scale score, absence of internal carotid artery occlusion, higher Alberta Stroke Program Early CT Score on CT, and absence of intravenous antihypertensives just before recombinant tissue plasminogen activator were independently related to a 3-month modified Rankin Scale score ≤1. Congestive heart failure and hyperglycemia were independently related to mortality.

Conclusions—Three-month outcomes of patients receiving low-dose intravenous recombinant tissue plasminogen activator therapy in the present study were similar to those from postmarketing surveys using 0.9 mg/kg alteplase. **(*Stroke*. 2009;40:3591-3595.)**

Key Words: acute stroke ■ alteplase ■ cerebral infarction ■ recombinant tissue plasminogen activator ■ stroke outcome ■ thrombolysis

In 2005, intravenous (IV) alteplase therapy at a dose of 0.6 mg/kg was approved in Japan after a dose comparison study using duteplase[1] and a multicenter study using a single dose of alteplase (Japan Alteplase Clinical Trial [J-ACT]),[2] although a head-to-head comparison of the alteplase dose of 0.9 mg/kg versus 0.6 mg/kg has not been done. A postmarketing survey from our single stroke center found that 36 (46%) of 78 patients receiving low-dose recombinant tissue plasminogen activator (rtPA) therapy had a favorable 3-month outcome corresponding to a modified Rankin Scale (mRS) score ≤1.[3]

Based on the large population of patients included in Western randomized, controlled trials and postmarketing

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studies, several predictors of stroke outcome after rtPA have been identified, including advanced age, stroke severity, initial hyperglycemia, and high acute blood pressure.[4–7] Low-dose rtPA therapy may, in principle, share the same predictors. Because MRI is widely available in Japan, studies on low-dose rtPA were often based on MRI and MR angiography. In the above study from our center, occlusion of the internal carotid artery (ICA) and early ischemic signs on diffusion-weighted MRI (DWI), defined as an Alberta Stroke Program Early CT Score (ASPECTS) ≤6, were independently predictive of an mRS ≥2 at 3 months.[3] Kimura et al[8] reported that ASPECTS on DWI ≤5 was predictive of a National Institutes of Health Stroke Scale (NIHSS) score≥20 at 7 days. Chronic outcomes of low-dose rtPA therapy as well as the factors affecting the outcomes should be ascertained using a larger population with a multicenter design.

To determine appropriate risk factor control in acute stroke, a multicenter study group (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] Study Group) was formed. A retrospective observational study was conducted to identify the effects of risk factors and other patient characteristics on the outcome of IV alteplase at a dose of 0.6 mg/kg. This article reports the overall general results.

Patients and Methods

The SAMURAI Study Group was composed of 10 Japanese stroke centers that were balanced regionally. In this study, all consecutive patients with ischemic stroke or transient ischemic attack who received IV rtPA therapy in these 10 centers between October 2005 (when IV alteplase therapy was approved in Japan) and July 2008 were registered. Patient eligibility for alteplase therapy was determined based primarily on Japanese guidelines for IV rtPA therapy,[9] which follow the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and J-ACT.[2,10] Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office.

Each patient received a single alteplase dose of 0.6 mg/kg (not exceeding 60 mg) IV with 10% given as a bolus within 3 hours of stroke onset followed by a continuous IV infusion of the remainder over 1 hour. Like in the NINDS study,[10] use of antithrombotic agents was prohibited in principle for 24 hours after onset, blood pressure was maintained at <180/105 mm Hg, and neurological signs and symptoms were frequently monitored.

Before rtPA therapy, all patients underwent brain noncontrast CT or DWI. The ASPECTS was calculated on both CT and DWI; it is a 10-point quantitative topographical scoring method of the early ischemic signs, originally developed for CT, which divides the middle cerebral arterial territory into 10 regions of interest.[11,12] To identify arterial occlusion sites, MR angiography, CT angiography, or ultrasound was performed. The baseline characteristics listed in Tables 1 and 2 were studied.

The outcomes were: completely independent activity of daily living at 3 months corresponding to an mRS ≤1; death at 3 months; any intracerebral hemorrhage (ICH) defined as CT evidence of new ICH within the initial 36 hours; and symptomatic ICH with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score. Symptomatic ICH was also defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[13] protocol as parenchymal hemorrhage Type II combined with an increase of ≥4 points from the baseline NIHSS score. Outcomes at 3 months were assessed by clinical examination at a hospital clinic (or by phone survey for patients whose neurological deficits were too severe to visit the clinic). The examiners at the clinics were familiar with patients' stroke features in some hospitals and not in others. For patients who were lost to follow-up at 3 months, mRS at hospital discharge was assessed instead.

Table 1. Baseline Characteristics and Physiological Data of 600 Patients

Demographics	
Male	377 (62.8%)
Age, years	72±12
Risk factors and comorbidities	
Hypertension	366 (61.0%)
Diabetes mellitus	110 (18.3%)
Dyslipidemia	125 (21.0%)
Atrial fibrillation	258 (43.4%)
Congestive heart failure (n=588)	51 (8.7%)
Prior ischemic stroke	109 (18.2%)
Premorbid mRS ≥2	65 (10.8%)
Prior ischemic heart disease	77 (13.1%)
Prior use of anticoagulants	53 (8.8%)
Prior use of antiplatelets	192 (32.0%)
Prior use of antihypertensives	265 (44.5%)
Prior use of statins	67 (11.2%)
Physiological data on admission	
Body weight, kg	58.7±11.9
Body height, cm (n=534)	160.1±8.9
Body mass index (n=534)	22.9±3.3
Systolic blood pressure, mm Hg	150.2±20.2
Diastolic blood pressure, mm Hg	81.4±15.4
Pulse rate, beats/min	79.7±19.4
Body temperature, °C	36.3±0.6
Blood glucose, mmol/L (n=585)	7.62±2.64
Total cholesterol, mmol/L (n=551)	4.88±1.03
Creatinine, mmol/L	81.0±66.8

Data are no. of patients (%) and means±SD for continuous variables.

Statistics

All calculations were performed using JMP 7 software (SAS Institute Inc). A probability value <0.05 was considered significant. The proportions and 95% CIs of patients with ICH and mRS ≤1 as well as mortality were calculated for all patients as well as for patients who met the criteria of the European license (patients ≤80 years old with an initial NIHSS score ≤24 and without any history of prior stroke and concomitant diabetes). Multivariate analyses were performed to find predictors for an mRS ≤1 and death at 3 months based on the characteristics 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. We assessed the main effects of each characteristic and did not assess bivariable interaction of characteristics. Multivariate analyses were also done simply with adjustment for sex, age, and initial NIHSS score.

Results

A total of 600 patients with stroke (377 men, 72±12 years old) were registered. During the same period, a domestic survey estimated that approximately 13 500 Japanese patients with stroke received IV rtPA therapy. Thus, the present patients accounted for approximately 4.4% of the rtPA-treated patients in Japan during that time period. Of these 600