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## Increasing use of intravenous rt-PA does not affect safety in acute stroke

**Abstract** *Background* Intravenous thrombolysis with rt-PA improves outcome in acute ischemic stroke. In a prospective study we analyzed the annual frequency of rt-PA treatment, its safety, and early clinical outcome. *Methods* All patients admitted to

our stroke unit (SU) from 1998 to 2003 were registered in a prospective data base. Documented data included patient age, sex, time interval until admission, initial therapy (e. g., thrombolysis), death, intracerebral hemorrhage, other complications, and score on the National Institute of Health Stroke Scale (NIHSS). *Results* From 1998 to 2003, a total of 112 patients were treated with systemic thrombolysis. The number of acute stroke patients admitted within 2.5 hours and therefore eligible for thrombolysis did not substantially change between 1998 and 2003. From 1998 to 2001 the percentage of acute stroke patients that received rt-PA was stable (12.6–16.9%). This percentage increased in 2002 (29.6%,  $p < 0.05$ ) and, again, in 2003 (42.1%,  $p < 0.01$ ). Of all treated patients, two developed symptomatic intra-

cerebral hemorrhage (1.8%) and five died three to seven days after thrombolysis (4.5%). The NIHSS score of patients receiving rt-PA significantly decreased during the acute treatment phase ( $14.2 \pm 5.1$  to  $8.0 \pm 5.9$ ,  $p < 0.001$ ). A comparison of single years revealed that this NIHSS score reduction was stable. *Conclusion* In our selected patients, the proportion of acute stroke patients treated with systemic thrombolysis increased almost three-fold from 1998 to 2003. This may be explained by protocol modifications and growing experience with the use of rt-PA. Our data demonstrate that increased use of rt-PA in acute stroke patients can be achieved without adversely affecting safety or clinical benefit.

**Key words** stroke · thrombolysis · safety

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### Introduction

Intravenous thrombolysis with rt-PA improves the outcome of acute stroke patients, if administered within three hours of symptom onset, even despite a ten-fold risk of symptomatic intracerebral hemorrhage [5]. Several multi-center series outside of prospective randomized trials have confirmed the beneficial effect of rt-PA in acute stroke [1, 3, 7].

Nevertheless, the percentage of acute stroke patients receiving intravenous thrombolysis is still quite small

[7]. This may be due to the limited time window for treatment and the strict inclusion/exclusion criteria. Another important factor may be physicians' reluctance to treat patients. Lack of experience with rt-PA and fear of adverse events may contribute to this reluctance [4].

To demonstrate developments in the delivery of thrombolysis, we analyzed the annual frequency of rt-PA treatment, its safety, and early clinical outcome in all acute stroke patients admitted to our stroke unit (SU) from 1998 to 2003.

## Methods

All patients admitted to our SU from 1998 to 2003 were registered in a prospective data base. Documented data included patient age, sex, time interval from symptom onset to admission, and initial therapy (e.g., thrombolysis). All patients receiving rt-PA had follow-up CT or underwent magnetic resonance imaging within 24 hours after treatment. In case of clinical deterioration, CT was repeated.

Death, intracerebral hemorrhage, malignant infarction, and other complications during the acute treatment phase were also documented. Symptomatic intracerebral hemorrhage (SIH) was defined as new signs of intracranial hemorrhage in follow-up CT with clinical deterioration of at least one point in the patient's score on the National Institute of Health Stroke Scale (NIHSS). The acute treatment phase was defined as the time the patient spent in our SU or, in case of referral, in our intensive care unit (ICU). By definition, the acute treatment phase ended, when the patient was discharged or referred to a regular ward or a rehabilitation center.

Intravenous thrombolysis was performed following a strict protocol that was modified in September 2002 immediately following the drug's approval by the European Union commission. Relevant changes in the protocol are specified in Table 1. The dose of rt-PA was 0.9 mg per kg body weight with a maximum of 90 mg. Ten percent was given as a bolus, the remaining 90 percent over one hour. Patients receiving intra-arterial thrombolysis were not included in our analysis.

As regards the time window of three hours, patients were considered potentially eligible for intravenous thrombolysis, if they were admitted within 2.5 hours after symptom onset. As the interval until admission was not reliably documented for all patients in 1998, exact data on the number of patients admitted within 2.5 hours cannot be provided for that year.

To compare the rate of treated patients in different years, repeated chi square tests were performed. To compare NIHSS scores on admission and discharge Student's linked t-tests were performed. To compare single parameters between different years, non-linked Student's t-tests were performed.

**Table 1** Relevant differences in the rt-PA treatment protocol before and after 09/2002

	1998–09/2002	09/2002–2003
age (years)	18–75	18–80
symptoms	hemispheric	suggesting MCA territory
severity	significant paresis and/or aphasia	score on NIHSS, 5–25
time window	3 hours	3 hours
exclusion criteria on CT	hemorrhage, infarction > 1/3 MCA territory	hemorrhage
confirmed vessel occlusion by TCD, CTA, MRA	required	not required
general exclusion criteria	according to NINDS study [5]	according to EU approval

MCA middle cerebral artery; NIHSS National Institute of Health Stroke Scale; CT computed tomography; TCD transcranial Doppler sonography; CTA CT angiography; MRA magnetic resonance angiography; NINDS National Institute of Neurological Disorders and Stroke; EU European Union

## Results

A total of 112 patients were treated from 1998 to 2003 with systemic thrombolysis. All patients had symptoms of acute hemispheric stroke, and therapy was started within three hours of symptom onset. Absolute numbers of treated patients were relatively stable from 1998 to 2001 but significantly increased in 2002 and, again, in 2003 (Table 2).

From 1998 to 2002, none of the treated patients developed SIH. In 2003, two patients had SIH (5%), both within one hour of thrombolysis. From 1998 to 2001, all patients survived the acute treatment phase. In 2002 two patients died (8.3%), both due to malignant infarction. In 2003 three patients died (7.5%), two due to malignant infarction, one due to SIH (Table 2).

Of all stroke unit patients, the percentage of patients admitted within the time window of 2.5 hours did not significantly change between 1999 and 2003 (Table 2). However, the percentage of treated patients significantly increased in 2002 and, again, in 2003 (Table 2, Fig. 1). In 2003, 40 of 95 stroke patients admitted within the time window of 2.5 hours received thrombolysis (42.1%).

Several factors contributed to this increase. Seven of the treated patients in 2003 were older than 75 years and would have been excluded before September 2002. Another seven patients in 2003 had no signs of major vessel occlusion, an exclusion criterion before September 2002. Conversely, the modification of the CT criteria had no effect on the rate of thrombolysis, since we did not see any patients with early ischemic signs affecting more than one third of the middle cerebral artery (MCA) territory within the three hour time window.

Criteria for admission to our SU did not change over the years. A subset of patients was referred to us from other hospitals after telephone contact with the clear target to perform thrombolysis. The number of patients that were accepted from these hospitals and actually treated with rt-PA did not substantially change over the years (exact numbers per single year: 3, 2, 5, 4, 6, 6 for 1998 to 2003).

Age and initial NIHSS scores of the patients receiving rt-PA remained stable (Table 2). Treated patients showed a significant NIHSS score reduction during the acute treatment phase (Table 2). A comparison of single years revealed no significant difference in this NIHSS score reduction (Table 2). The duration of the acute treatment phase did not significantly change over the years (Table 2).

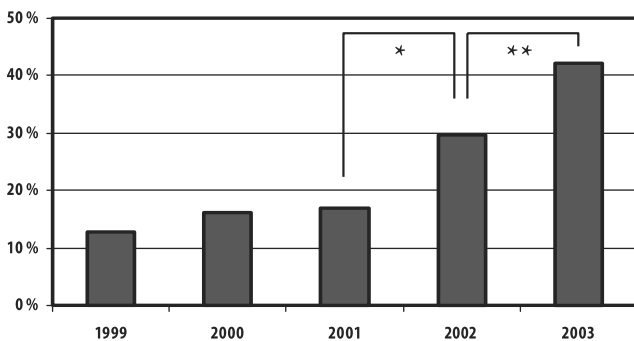
## Discussion

This single center study demonstrates that thrombolysis was increasingly administered for acute stroke from 1998 to 2003. The number of stroke patients admitted

**Table 2** Patient data and outcome parameters after rt-PA treatment in acute stroke

year	1998	1999	2000	2001	2002	2003	1998–2003
pts. treated with rt-PA	9	11	15	13	24	40	112
mean age (years)	60.9±8.5	55.1±15.0	67.2±11.5	64.2±11.7	66.5±9.6	65.6±12.0	64.4±11.8
male sex (%)	77.8	63.6	60.0	53.8	58.3	67.5	63.4
SIH	0	0	0	0	0	2 (5%)	2 (1.8%)
death	0	0	0	0	2 (8.3%)	3 (7.5%)	5 (4.5%)
pts. admitted ≤2.5 hours	no data*	87	93	77	81	95	no data*
pts. treated vs. admitted ≤2.5h (%)	no data*	12.6	16.1	16.9	29.6	42.1	no data*
score on NIHSS at admission	13.3±5.4	14.5±4.1	15.3±7.1	13.3±4.8	17.0±4.6	12.5±4.1	14.2±5.1
score on NIHSS at discharge	4.6±2.5	8.7±6.6	7.5±8.6	9.2±6.6	9.8±5.5	7.3±4.8	8.0±5.9
NIHSS score difference	8.8±4.6	5.7±6.0	7.8±7.9	4.1±6.1	7.1±5.1	5.1±4.6	6.2±5.7
acute treatment phase (days)	4.8±2.7	9.6±8.4	5.6±2.9	10.4±7.8	7.5±5.3	8.1±4.2	7.8±5.4

SIH symptomatic intracerebral hemorrhage. \* in 1998 the number of patients admitted within 2.5 hours was not documented



**Fig. 1** Percentage of acute stroke patients (admission within 2.5 hours) that received rt-PA. \*  $p < 0.05$ ; \*\*  $p < 0.01$

within a time window feasible for thrombolysis remained stable over the years. However, the rate of treated patients rose substantially in 2002 and 2003. Several factors may have contributed to this development.

First, the modification of our stroke protocol in September 2002 had a clear impact on the rate of thrombolysis. Inclusion of older patients and inclusion of patients without evidence of major vessel occlusion can in part explain the increasing numbers.

Second, the frequency of rt-PA treatment may have been affected by the official approval of the drug for acute stroke by the federal German authorities in April 2000 and the European Union commission in September 2002. Before approval, the physicians' reluctance to use an off-label drug and difficulties in obtaining informed consent may have prevented many patients from being treated. After approval, physicians may have felt more motivated and even obliged to use rt-PA, unless the drug was clearly contraindicated.

The overall rate of severe complications was very low (2/112 SIH, 5/112 deaths). None of our 48 patients treated between 1998 and 2001 died or experienced SIH within the acute treatment phase. This surprising find-

ing may be explained by the low number of patients and the very careful selection of patients for treatment. Despite the increasing administration of rt-PA in 2002 and 2003, complications did not exceed the expected rates. In the year 2003, the year with the highest rate of treated patients, SIH occurred in 2/40 cases (5%). This number is comparable to the National Institute of Neurological Disorders and Stroke (NINDS) trial, in which 6.4% of patients experienced SIH within 36 hours after therapy [5].

Of five patients with fatal outcome, one died from SIH. The other four died from massive hemispheric edema three to seven days after thrombolytic therapy following large hemispheric infarction. A causal relationship between rt-PA treatment and malignant infarction cannot be excluded. One can speculate that neurotoxic effects of rt-PA [6, 8] or reperfusion injury after successful recanalization [2] may have aggravated the ischemic damage in these patients.

The rate of thrombolysis can be influenced by inclusion of patients with less or more severe neurological deficits. However, in our patients, the mean baseline NIHSS score and its standard deviation were quite stable over the years. They were comparable to the baseline scores in the NINDS trial, in which the NIHSS score decreased 24 hours after treatment from a median of 14 at baseline to 8 [5]. The mean NIHSS scores of our patients decreased from 14.2 to 8.0 within the acute treatment phase of several days. This clinical improvement was not attenuated by the increasing rate of treated patients.

As a single center, we were able to substantially increase the rate of thrombolysis over the last six years. At present, about 40% of our acute stroke patients who are admitted within 2.5 hours after symptom onset are treated with intravenous rt-PA. These data suggest that low complication rates and favorable clinical outcome can be maintained while increasing the use of rt-PA.

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