The Role of Thrombolysis in Acute Ischemic Stroke

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Abstract
Up to the mid-1990s, the treatment of acute ischemic stroke was almost anecdotal. The introduction of systemic thrombolysis dramatically changed the scenario improving patient outcomes and becoming the standard of care for patients who present within 3 h from the onset of symptoms. Other options, such as intraarterial thrombolysis, or different mechanical reperfusion approaches, have been tested in the past few years. The benefit-risk profile of these approaches is discussed in this review.

The current main challenge in the therapy of acute stroke is to define the optimal strategy for patients excluded from thrombolysis because of delayed presentation or older age and for patients treated with thrombolysis that do not reperfuse.

Die Rolle der Thrombolyse bei akutem ischämischem Schlaganfall

Zusammenfassung
Bis in die 90er Jahre des letzten Jahrhunderts war die Behandlung des akuten ischämischem Schlaganfalls nahezu anekdotisch. Durch die Einführung der systemischen Thrombolyse haben sich die Lage dramatisch verändert und die Prognose der Patienten deutlich verbessert. Mittlerweile ist diese Form der Behandlung zum Therapiestandard bei Patienten innerhalb von 3 h nach Symptombeginn geworden. Andere Therapieoptionen, etwa die intraarterielle Thrombolyse oder verschiedene mechanische Ansätze zur Reperfusion, sind in den vergangenen Jahren erprobt worden. Das Nutzen-Risiko-Profil dieser Therapieansätze wird im vorliegenden Artikel diskutiert.

Die derzeit größte Herausforderung in der Behandlung des akuten Schlaganfalls besteht in der Festlegung der optimalen Therapie für Patienten, bei denen wegen verspäteter Vorstellung oder höheren Alters eine Thrombolyse nicht möglich ist, oder für Patienten, bei denen es nach erfolgter Thrombolyse zu keiner Reperfusion gekommen ist.

Introduction
In the USA, more than 700,000 adults have a stroke every year, with nearly 200,000 suffering a recurrent event. The risk of stroke increases exponentially with age [1]. Stroke is the third cause of death in the USA and the leading cause of severe disability in the American adult population [2]. Similarly, in Europe, stroke is the first cause of severe disability and accounts for 10–12% of all deaths (400,000 deaths per year). In Italy, stroke prevalence increases from 4% among patients aged 65–70 years to 10% in those aged 80–85 years [3].

Stroke is defined as the abrupt onset of a focal or global neurologic deficit, related to cerebrovascular causes, lasting at least 24 h or leading to death. It is a syndrome due to multiple etiologies and characterized by various neurologic manifestations which are related to the location and extension of brain injury. The vast majority of strokes are ischemic due to the occlusion of arteries that deliver essential nutrients and oxygen to the brain.

Until the 1990s, acute stroke treatment was limited to antithrombotic therapy and management of life-threatening complications such as aspiration pneumonia, venous thromboembolisms, severe hyperthermia, and cerebral edema. This approach was unable to significantly modify the short- and long-term mortality and disability of the disease. To improve these outcomes, much effort has been spent in finding new, more effective treatments for acute stroke.

The rationale for thrombolytic therapy was based on the observation that the majority of ischemic strokes were the consequence of thrombotic or thromboembolic arterial occlusions [4]. Angiographic studies demonstrated the presence of occlusive clots in up to 80% of ischemic strokes [5]. In the remaining 20% of stroke events, the putative underlying mechanism was a microthrombus not detected by angiogram or thrombotic occlusions spontaneously recanalized.

In the past 10 years, different approaches have been evaluated to optimize thrombolysis in clinical practice: evidence of efficacy and safety of these different strategies, alone or in combination, are discussed in the present review:
• systemic intravenous injection of several fibrinolytic drugs such as streptokinase, alteplase, tenecteplase, and desmoteplase;
• intraarterial thrombolysis with direct administration of thrombolytic agents to the area of the occlusion;
• mechanical recanalization with clot-removing devices, balloons, and stents.

Intravenous Thrombolysis

Intravenous thrombolysis for acute ischemic stroke is, today, considered the therapy of choice for acute ischemic stroke for eligible patients (Tables 1 and 2). The US Food and Drug Administration (FDA) approved the use of alteplase in 1996 on the basis of the National Institute of Neurological Disorders and Stroke (NINDS) trial results [6]. Furthermore, the American Stroke Association guidelines currently recommend alteplase as first-line treatment for patients with acute ischemic stroke [7]. For eligible patients, the guidelines recommend the administration of intravenous (i.v.) recombinant tissue-type plasminogen activator (rtPA) at a dose of 0.9 mg/kg (maximum of 90 mg), with 10% of the total dose administered as an initial bolus over 1 min, and the remaining dose infused in < 1 h. To qualify for i.v. thrombolysis, the patient should get started on the treatment within 3 h from symptom onset (Table 2). The European Union (EU) approved i.v. thrombolysis with rtPA in 2002.

Randomized Trials with rtPA

The NINDS study, which enrolled 625 patients randomly assigned to placebo or i.v. rtPA at the above-mentioned dose to treat ischemic stroke within 3 h from the onset of symptoms, is, at present, the only large randomized clinical trial that clearly proved benefit of rtPA in acute ischemic stroke [6]. Primary outcomes measures were the complete resolution of symptoms or a four-point improvement on the National Institute of Health Stroke Scale (NIHSS) Score at 24 h or 3 months from treatment. Although no significant benefit was noticed within the first 24 h of treatment (there was just a trend in favor of the group treated with rtPA), there was an 11% absolute increase in the number of patients with little or no deficits among those receiving rtPA compared with those receiving placebo at 3 months. Although the treatment window was 3 h, patients who received thrombolytic therapy within 90 min had better outcomes compared to those treated within 90–180 min from symptom onset. The benefit of rtPA persisted despite the significant higher rate of symptomatic intracerebral hemorrhage in the first 36 h among rtPA recipients (6.4% vs. 0.6%). Up to 3 months, no difference in mortality between the two groups was observed (Figure 1).

Further randomized clinical trials designed with the aim of widening the therapeutic window or test the effect of higher doses of rtPA failed. In the European Cooperative Acute Stroke Study (ECASS), 620 patients with an acute ischemic stroke were randomized to receive a higher dose of intravenous rtPA (1.1 mg/kg) or placebo within 6 h from stroke onset [8]. Compared to those in the placebo group, patients treated with rtPA had a statistically significantly higher incidence of parenchymal hemorrhage (19.8% vs. 6.5%) and no significant benefit in terms of neurologic outcome.

The same authors have then designed the ECASS II trial, which randomized 800 patients with acute ischemic stroke to receive intravenous rtPA at a dose of 0.9 mg/kg (same dose used in the NINDS trial) or placebo within 6 h of symptom onset [9]. Again, the results showed no significant benefit for patients treated with rtPA at the end of 90 days. A post hoc analysis, however, suggested a benefit among patients treated within 3 h from stroke onset, supporting the findings of the NINDS trial.

In the Alteplase ThromboLysis for Acute Non-interventional Therapy in Ischemic Stroke study (ATLANTIS), 547 patients were randomized to treatment with intravenous rtPA at a dose of 0.9 mg/kg or placebo within 3–5 h after symptom onset [10]. There was no significant benefit of rtPA treatment versus placebo with respect to the neurologic recovery, but there was a significantly increased risk

**Figure 1.** Survival curves in patients with acute ischemic stroke receiving intravenous rtPA or placebo in the NINDS study (modified from [6]).

**Abbildung 1.** Überlebenskurven von Patienten mit akutem Schlaganfall nach Behandlung mit intravenös appliziertem rtPA oder Plazebo (modifiziert nach [6]).

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