Treatment of Acute Ischemic Stroke: Recent Progress
Norio Tanahashi and Yasuo Fukuuchi

Abstract

Intravenous thrombolysis with tissue plasminogen activator is currently the most effective treatment of acute ischemic stroke if administered within 3 hours after symptom onset. Intraarterial thrombolysis by prourokinase is another choice if the middle cerebral artery is occluded and within less than 6 hours after onset. Although heparin, especially a moderate dose, is not proved to be effective, a randomized, placebo-controlled trial to determine the safety and efficacy of argatroban (a selective thrombin inhibitor) in patients with acute ischemic stroke was started in USA. Aspirin provides some benefit to patients with acute stroke. However, its effect is not fully satisfactory. Although reports of numerous trials for neuroprotective drugs have been disappointing, edaravone (free radical scavenger) was approved for the treatment of acute ischemic stroke in Japan. In the future, thrombolytic and neuroprotective drugs will be used in combination.

Intravenous Thrombolytic Therapy

Table 1 shows the findings of four large, randomized trials of intravenous tPA in acute ischemic stroke (1-6). The study supported by the National Institute of Neurological Disorders and Stroke (NINDS) (1) was pivotal in that intravenous tPA became the first treatment for acute ischemic stroke to be approved by the FDA. The trial had two parts. In both parts of the study, patients were randomized to receive placebo or tPA at 0.9 mg/kg of body weight (maximum of 90 mg), 10% of which was given as a bolus, followed by the remaining 90% as a constant infusion over a period of 60 minutes. The characteristics of patients with stroke who may be eligible for intravenous tPA were as follows: age < 18 year, diagnosis of ischemic stroke causing clinically apparent neurologic deficit, onset of symptoms < 3 hour before possible beginning of treatment, no history of intracranial hemorrhage, systolic blood pressure < 185 mmHg, diastolic blood pressure < 110 mmHg, no rapidly resolving symptoms or only minor symptoms of stroke, and so on. Like the European Cooperative Acute Stroke Study (ECASS) (2), a head CT scan was required, but unlike ECASS, the only CT exclusion criterion in the NINDS study was evidence of intracranial hemorrhage. Part 1 (in which 291 patients were enrolled) tested whether tPA had clinical activity, as indicated by an improvement of 4 points over baseline values in the score of the National Institutes of Health Stroke Scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS. In part 1, there was no significant difference between the group given tPA and that given placebo in the percentages of patients with favorable outcome measures. In part 2, the long-term clinical benefit of tPA predicted by the results of part 1 was confirmed (global odds...

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Table 1. Randomized Trials of Intravenous Thrombolysis by tPA for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Time window, h</th>
<th>Treatment group</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECASS (2)</td>
<td>620</td>
<td>0-6</td>
<td>1.1 mg IV tPA vs placebo</td>
<td>No difference in BI or MRS at 90 d</td>
</tr>
<tr>
<td>NINDS part 1 (1)</td>
<td>261</td>
<td>0-3</td>
<td>IV tPA at 0.9 mg/kg (maximum 90 mg) vs placebo</td>
<td>No difference in ratio of improvement in NIHSS at 24 h</td>
</tr>
<tr>
<td>NINDS part 2 (1)</td>
<td>333</td>
<td>0-3</td>
<td>IV tPA at 0.9 mg/kg (maximum 90 mg) vs placebo</td>
<td>The odds ratio for a favorable outcome at 3 mo after stroke was 1.7 (95% CI, 1.2–2.6; p=0.008)</td>
</tr>
<tr>
<td>ECASS II (3)</td>
<td>800</td>
<td>0-6</td>
<td>IV tPA at 0.9 mg/kg (maximum 90 mg) vs placebo</td>
<td>No significant difference in favorable MRS at 90 d with MRS dichotomized at 1–2 (primary endpoint), TPA group had a significantly higher rate of favorable outcome with MRS dichotomized at 2–3.</td>
</tr>
<tr>
<td>ATLANTIS (4)</td>
<td>613</td>
<td>3-6</td>
<td>IV tPA at 0.9 mg/kg (maximum 90 mg) vs placebo</td>
<td>No significant difference in the proportion of patients achieving NIHSS score of 0 or 1 at 90 d (primary outcome measure). Rate of 10 d symptomatic and fatal ICH were greater in the tPA group.</td>
</tr>
<tr>
<td>TTAISS (5)</td>
<td>142</td>
<td>0-6</td>
<td>IV tPA at 0.9mg/kg (maximum 90 mg) vs placebo</td>
<td>Rate of 4-point NIHSS score improvement at 24 h was significantly greater in the tPA group, but significantly less at 30 d.</td>
</tr>
</tbody>
</table>


ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with tPA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given tPA but only 0.6 percent of patients given placebo (p<0.001). Mortality at three months was 17 percent in the tPA group and 21 percent in the placebo group (p=0.30).

In three other large trials [ECASS (2), ECASS II (3), and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) (4) trial, the Thrombolytic Therapy in Acute Ischemic Stroke Study (TTAISS) (5)], there was no significant rtPA benefit on the 90-day efficacy endpoints. The risk of symptomatic ICH increased with rtPA treatment. The negative results of ECASS, ECASS II, and the ATLANTIS trial may be due to the fact that the patients involved were treated much later than those in the NINDS rtPA Stroke Study. Therefore, the therapeutic time window of intravenous tPA for acute ischemic stroke is considered to be within 3 hours after onset. Recent case studies (7–14) indicated that implementation of intravenous tPA therapy may not always be easy and safe, but other series suggested that the safety and efficacy of this treatment were similar to those in both parts of the NINDS rtPA Stroke Study. In addition, intravenous tPA was found to be cost effective in an analysis of the patients in the NINDS rtPA Stroke Study. This treatment is not approved in Japan.

**Intraarterial Thrombolytic Therapy**

Local intraarterial thrombolysis performed with a microcatheter that is placed into, beyond, and proximal to an arterial occlusion is used worldwide on the basis of the results of randomized trials (Table 2) (15–17) and numerous case series. In the past, the agents most commonly studied was urokinase; intraarterial tPA and prourokinase have mainly been used in recent investigational studies. Approximately 40 percent of the patients who undergo this treatment have complete arterial recanalization, and approximately 35 percent have partial recanalization. These rates of recanalization are higher than those with intravenous thrombolytic therapy. The largest randomized trial of the three, the Prolyse in acute Cerebral Thromboembolism II (PROACT II) trial (17), a total of 180 patients with acute ischemic stroke within 6 hours caused by angiographically proven occlusion of the MCA and without hemorrhage or major early infarction signs on computed tomographic scan were enrolled. Patients were randomized to receive 9 mg of IA r-
Table 2. Randomized Trials of Intraarterial Thrombolysis for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Time window, h</th>
<th>Treatment groups</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMS (15)</td>
<td>35</td>
<td>3</td>
<td>IV tPA at 0.6 mg/kg of body weight (60 mg max), 10% bolus with remainder over 30 min followed by tPA at 10 mg/h up to 20 mg or placebo followed by IA tPA at 10 mg/h up to 20 mg</td>
<td>No difference in BI or MRS at 90 d</td>
</tr>
<tr>
<td>PROACT (16)</td>
<td>46</td>
<td>6</td>
<td>6 mg IA r-pro-UK and IV heparin or sham IA and IV heparin</td>
<td>Recanalization was associated with r-pro-UK (p=0.017)</td>
</tr>
<tr>
<td>PROACT II (17)</td>
<td>180</td>
<td>6</td>
<td>9 mg IA r-pro-UK and IV heparin or IV heparin only</td>
<td>40% of r-pro-UK group and 25% of control group had slight or no neurologic disability at 90 d (p&lt;0.04)</td>
</tr>
</tbody>
</table>


pro-UK plus heparin (n=121) or heparin only (n=59). The primary outcome, analyzed by intention-to-treat, was based on the proportion of patients with slight or no neurological disability at 90 days as defined by a modified Rankin score of 2 or less. Secondary outcomes included MCA recanalization, the frequency of intracranial hemorrhage with neurological deterioration, and mortality. In the primary analysis, 40% of r-pro-UK patients and 25% of control patients had a modified Rankin score of 2 or less (p=0.04). Mortality was 25% for the r-pro-UK group and 27% for the control group. The recanalization rate was 66% for the r-pro-UK group and 18% for the control group (p<0.001). Intracranial hemorrhage with neurological deterioration within 24 hours occurred in 10% of r-pro-UK patients and 2% of control patients (p=0.06). Despite an increased frequency of early symptomatic intracranial hemorrhage, treatment with IA r-pro-UK within 6 hours of the onset of acute ischemic stroke caused by MCA occlusion significantly improved clinical outcome at 90 days. PROACT II is the best evidence to date supporting the efficacy intra-arterial thrombolysis up to 6 hours. Pro-UK is not currently approved for use in the United States. PROACT III is currently underway.

Intraarterial thrombolysis has not been directly compared with intravenous thrombolysis, thus the relative merits of these two routes of therapy in patients with acute ischemic stroke remains unknown.

Recently, new MRI techniques have become available that allow early identification of ischemic brain regions and cerebral perfusion deficits. Diffusion-weighted imaging (DWI) can rapidly detect ischemic brain lesions, and perfusion-weighted imaging (PWI) can identify blood flow abnormalities. It is considered that the mismatch between the acute PWI lesions and smaller DWI lesion represents potentially salvageable brain tissue (an estimate of the ischemic penumbra), and in patients with a PWI/DWI mismatch, early reperfusion is often associated with substantial clinical improvement and reversal or reduction of DWI lesion growth (18).

Antithrombotic and Antiplatelet Drugs

Heparins and heparinoids

Unfractionated (UF) heparin has been used for decades in the treatment of ischemic stroke, but its use remains controversial. In the International Stroke Trial (IST) (19), 19,435 patients within 48 hours of ischemic stroke onset were randomly assigned to receive 12,500 U subcutaneous UF heparin twice daily, 5,000 U subcutaneous UF heparin, or no heparin for 14 days and aspirin or no aspirin in a 3x2 factorial design. Among heparin-allocated patients, there were non-significantly fewer deaths within 14 days (876 [9.0%] heparin vs 905 [9.3%] no heparin), corresponding to 3 (SD 4) fewer deaths per 1,000 patients. At 6 months the percentage dead or dependent was identical in both groups (62.9%). Patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9% vs 3.8%) but this was offset by a similar-sized increase in hemorrhagic strokes (1.2% vs 0.4%), so the difference in death or non-fatal recurrent stroke (11.7% vs 12.0%) was not significant. Heparin was associated with a significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1,000. Compared with 5,000 IU bd heparin, 12,500 IU bd heparin was associated with significantly more transfused or fatal extracranial bleeds, more hemorrhagic strokes, and more deaths or non-fatal strokes within 14 days (12.6% vs 10.8%). However, the activated partial-thromboplastin time was not monitored, and one-third of the patients were treated before a CT scan of the head was obtained to rule out the possibility of brain hemorrhage. More recent estimates of recurrence rates for cardioembolic stroke have been in the range of 1% to 2% per week (20). Given the lower risk for early recurrent embo-
lism and the greater risk for early hemorrhagic transformation in cardioembolic stroke, the routine use of heparin in presumed cardioembolic stroke cannot be recommended and should be reserved for cases in which a clear embolic source is identified (e.g., actively mobile or mural thrombus) (21). Recent mega trials for stroke indicate that the risk for early recurrent stroke in the general stroke population is also low (1.07 recurrent stroke per 100 patients per week), obviating the previously perceived need for urgent anticoagulation with heparin (22).

**Low molecular weight heparins and heparinoids**

Low molecular weight heparin (LMWH) is derived enzymatically or chemically from UF heparin but the two differ in their mode of action. UF heparin exerts its anticoagulant effect by activating antithrombin III and thereby inhibiting thrombin and, to an extent, activated factor X (factor Xa). In contrast, LMWH preferentially inhibits factor Xa rather than thrombin. Low molecular weight heparinoids are glycosaminoglycans, which differ from heparins in that their anticoagulant activity is due to their components: heparin sulfate, dermatan sulfate, and chondroitin sulfate. These factors catalyze the inhibitory effect of heparin cofactor II on thrombin and have a higher anti-Xa/anti-IIa activity ratio than LMWH. In one randomized trial of LMWH for acute ischemic stroke (23), 306 stroke patients who presented within 48 hours of symptom onset were randomized to receive high-dose vs low-dose LMWH (Nadroparin) or placebo for 10 days. The primary endpoint was poor outcome defined as death or dependency at 6 months, with the same outcome at the 3 month secondary endpoint. No significant difference in outcome was seen at 3 months; however, at 6 months, there was a significant dose-dependent reduction in the percentage of patients left dead or dependent in favor of high-dose nadroparin (p=0.005). There was no difference between the groups with regard to hemorrhagic transformation or systemic bleeding complications. This result was not confirmed in a larger trial using flaxiparine (24), which involved 750 patients. ORG 10172 (danaproid) is the haparinoid that has been most extensively studied in acute ischemic stroke. In the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) (20), 1,281 patients with ischemic stroke who presented within 24 hours of symptom onset were randomized to receive either the drug or placebo intravenously for 7 days. The primary outcome measure was dichotomized favorable outcome on the GOS and BI at 3 months. No difference between the groups was seen, although subgroup analysis did suggest benefit to treatment with ORG 10172 in patients with presumed large artery atherothrombotic stroke. The rate of major bleeding events, including ICH, was significantly higher in patients treated with ORG 172 (p=0.05).

**Argatroban**

Argatroban, a selective thrombin inhibitor, was developed in Japan. It has been demonstrated to be effective for atherothrombotic stroke within 48 hours after onset with a low incidence of hemorrhagic complications (25). Its use was approved in Japan since 1996. Argatroban specifically binds to the active site of thrombin to inhibit its action. It is administered by intravenous drip infusion for 7 days (at a daily dose of 60 mg for the first 2 days and a daily dose of 20 mg for the next 5 days). Unlike UF heparin, which is associated with considerable individual differences in efficacy and which is difficult to control, argatroban exerts a prompt stable antithrombin action and in a dose-dependent manner after infusion. Another advantage of argatroban is that it acts on a clot-binding thrombin, whereas heparin does not. In the USA, a randomized, placebo-controlled, three treatment arm study to determine the safety and efficacy of argatroban injection in patients with acute ischemic stroke (ARGIS-1) was started. The treatment window is 12 hours of onset of symptoms.

**Antiplatelet Agents**

**Aspirin**

The role of aspirin as acute stroke therapy was evaluated in two large trials. In the IST (19), there were non-significantly fewer deaths within 14 days [872 (9.0%) vs 909 (9.4%)], corresponding to 4 (SD 4) fewer deaths per 1,000 patients among aspirin-allocated patients. At 6 months there was a non-significant trend towards a smaller percentage of the aspirin group being dead or dependent (62.2% vs 63.5%, 2p=0.07), a difference of 13 (SD 7) per 1,000; after adjustment for baseline prognosis the benefit from aspirin was significant [14 (SD 6) per 1,000, 2p=0.03]. Aspirin-allocated patients had significantly fewer recurrent ischemic strokes within 14 days (2.8% vs 3.9%) with no significant excess of hemorrhagic strokes (0.9% vs 0.8%), so the reduction in death or non-fatal recurrent stroke with aspirin (11.3% vs 12.4%) was significant. Aspirin was associated with a significant excess of 5 (SD 1) transfused or fatal extracranial bleeds per 1,000; in the absence of heparin the excess was 2 (SD 1) and was not significant. The Chinese Acute Stroke Trial (CAST) (26) was a multicenter, randomized, double-blind, placebo-controlled trial of 21,106 patients with acute ischemic stroke who presented within 48 hours of symptom onset. Patients received either 160 mg of aspirin or placebo daily for 4 weeks. The primary endpoints were death in hospital (up to 4 weeks after stroke) or death or disability at discharge. There was a significant 14% (SD 7) proportional reduction in mortality during the scheduled treatment period [343 (3.3%) deaths among aspirin-allocated patients vs 398 (3.9%) deaths among placebo-allocated patients; 2p=0.04]. There were significantly fewer recurrent ischemic strokes in the aspirin-allocated than in the placebo-allocated group [167 (1.6%) vs 215 (2.1%); 2p=0.01] but slightly more hemorrhagic strokes [115 (1.1%) vs 93 (0.9%); 2p>0.1]. For the combined in-hospital endpoint of death or non-fatal stroke at 4 weeks, there was a 12% (6) proportional risk reduction with aspirin (545 [5.3%] vs 614 [5.9%]; 2p=0.03), an absolute difference of 6.8 (3.2) fewer cases per 1,000. At discharge, 3,153 (30.5%) aspirin-allocated patients and 3,266 (31.6%) placebo-allocated patients were dead or dependent, corresponding to 11.4 (6.4) fewer per 1,000 in favor of aspirin (2p=0.08). Although the absolute risk reduction for recurrent ischemic stroke in the IST and CAST studies was only 1% to 2%, the results were statis-
tically significant and do indicate that aspirin is beneficial in the treatment of acute stroke. A combined analysis of 40,000 randomized patients from CAST and IST (27) was done to assess the balance of benefits and risk of aspirin in particular categories of patients with acute stroke (e.g., the elderly, those without a CT scan, or those with atrial fibrillation) and showed that early aspirin is beneficial for a wide range of patients, and its prompt use should be routinely considered for all patients with suspected acute ischemic stroke, mainly to reduce the early recurrence. Figure 1 shows the absolute effect in CAST and IST of the early use of aspirin in 40,000 randomized patients with suspected ischemic stroke.

**Sodium ozagrel**

Sodium ozagrel, selective thromboxane A2 synthesis inhibitor, is proven to be effective for patients with cerebral thrombosis within 5 days after symptom onset in Japan and is currently available (28). Thromboxane A2 is known to increase following ischemic stroke. It has a vasoconstrictive action as well as a platelet-aggregation action. The incidence of hemorrhagic complication is much lower with sodium ozagrel therapy than with thrombolytic therapy. A large scale of randomized controlled study will be needed to confirm its efficacy.

**Abciximab**

The mechanisms of all platelet activation and aggregation share a final common pathway dependent on the surface glycoprotein IIb/IIIa complex (GP IIb/IIIa). The results of a Phase II dose-escalation safety study of the GP IIb/IIIa receptor inhibitor (29), abciximab, have been reported. The data suggested a trend toward better outcome with abciximab. A multicenter Phase III trial of abciximab for acute ischemic stroke is currently underway.

**Defibrinogenating agents**

The defibrinogenating agent, ancrod, is extracted from the venom of the Malayan pit viper. Ancrod converts fibrinogen into soluble fibrin products, with a subsequent decrease in the plasma concentration of fibrinogen and depletion of the substrate needed for thrombus formation. In the Stroke Treatment with Ancrod Trial (STAT) (30), 500 patients with ischemic stroke who presented within 3 hours of symptom onset were randomized to receive a 3-day infusion of ancrod followed by bolus infusions on days 4 and 5, with all doses adjusted according to the fibrinogen level, or placebo. Total or near-total recovery at three months was achieved in 42 percent of the patients given ancrod, as compared with 34 percent of those

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**Figure 1. Absolute effects in CAST and IST of early use of aspirin in 40,000 randomized patients with suspected acute ischemic stroke.** Numbers and percentages of patients with various outcomes during the scheduled treatment period, by allocated treatment. The percentages are plotted as bars (with the SD of each bar plotted at the top). The difference between aspirin and control is given as the benefit per 1,000, along with its SD and statistical significance (2p). A negative benefit indicates an apparent hazard. *Number of patients who experienced the relevant event and survived.
Table 3. Recently Completed and Ongoing Clinical Trials of Neuroprotective Agents for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Agent</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate antagonists</td>
<td>CGS 19755</td>
<td>Competitive NMDA antagonist</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td></td>
<td>YM-872</td>
<td>AMPA receptor antagonist</td>
<td>II/III</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Apiganel</td>
<td>NMDA channel blocker</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td>NMDA receptor antagonist</td>
<td>III</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>GV 150526</td>
<td>NMDA (glycine-site) antagonist</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td>Voltage-gated calcium-channel agonist</td>
<td>Nimodipine</td>
<td>Reduction of Ca(^{2+}) influx</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td>Voltage-dependent potassium-channel agonist</td>
<td>BMS-204352</td>
<td>Reduction of Ca(^{2+}) influx</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td>Sodium-channel agonist</td>
<td>Fosphenytoin</td>
<td>Reduction of excitation and glutamate release</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td>Serotonin receptor agonist</td>
<td>Repinotan</td>
<td>Reduction of excitation and glutamate release</td>
<td>III</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GABA agonist</td>
<td>Clomethiazole</td>
<td>Reduction of excitation and glutamate release</td>
<td>III</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Free radical scavengers</td>
<td>Tirilazad</td>
<td>Reduction of free-radical injury</td>
<td>III</td>
<td>No efficacy</td>
</tr>
<tr>
<td></td>
<td>Ebselen</td>
<td></td>
<td>III</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Edaravone</td>
<td></td>
<td>III</td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td>NXY-059</td>
<td></td>
<td>II</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Astrocyte inhibitor</td>
<td>ONO-2506</td>
<td></td>
<td>II</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NO donor</td>
<td>Nitroglycerin</td>
<td>Reduction of glutamate release or reduction of NO mediated injury</td>
<td>II/III</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NO blocker</td>
<td>Lubeluzole</td>
<td></td>
<td>III</td>
<td>No efficacy</td>
</tr>
</tbody>
</table>

AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, GABA: γ-aminobutyric acid, NMDA: N-methyl-D-aspartate.

given placebo (p=0.04). The rate of symptomatic ICH was 5.2% with ancred, as compared with 2.0% with placebo (p=0.001). Further evaluation of the preliminary STAT data will be necessary in the future.

Neuroprotective Agents

Neuroprotective agents are potential stroke treatments that function to protect ischemic brain cells. The neuroprotective agents focus on the penumbra region of the stroke, where the cells are dysfunctional due to ischemia but not irreversibly injured like the cells in the core of the stroke. Neuroprotective agents may be able to extend the thrombolytic time window. These neuroprotective efforts target common mechanisms of ischemic tissue injury such as cellular Ca\(^{2+}\) overload, the generation of reactive oxygen species, the activation of catabolic or energy-depleting enzymes, and apoptosis, or inflammation (31–33). However, the larger part of the effort to reduce brain vulnerability to ischemic injury has primarily focused on attenuating excitotoxicity. The results of neuroprotective clinical trials to date have been disappointing despite the promising results of earlier animal studies (Table 3). The observed lack of efficacy of these drugs may be due to the narrow time window, inadequate doses, inadequate drug penetration, adverse effects, evaluation of efficacy which might be less sensitive than markers of infarct volume or histopathology, or morphological and functional differences between the brain of humans and animals (34, 35). Since receptor-rich cortical tissue, upon which some neuroprotective agents act, is not involved by ischemia in all stroke patients, the variability of clinical stroke may lessen treatment effects as a whole. The use of newer MRI techniques may be helpful in the selection of a homogeneous population and in measuring efficacy. Moreover, arterial occlusion and inadequate circulation in collateral vessels may preclude adequate delivery of the drug to a substantial portion of the ischemic tissue. However, there are many promising cytoprotective and antiexcitotoxic approaches to reducing ischemic brain damage still in the development pipeline.

Recently, edaravone, a novel free radical scavenger, was approved for use in patients with acute ischemic stroke within 24 hours after onset in Japan (unpublished observation).

On theoretical grounds, antioxidant drugs might be especially valuable in reducing reperfusion-induced injury, for example in association with thrombolytic therapy. A combination of reperfusion with a cocktail of carefully selected neuroprotective drugs will become a first line of treatment of acute ischemic stroke.

Conclusions

We have many strategies to choose for the treatment of acute ischemic stroke. The choice of treatment must rely on the accurate information of time after symptom onset, severity, CT findings, level of blood pressure, etc. New MRI techniques like
diffusion-weighted imaging, perfusion-weighted imaging or MR angiography will help the doctor’s decision making of the treatment in the early phase of acute ischemic stroke. Intravenous thrombolysis with tPA is currently the most effective treatment if administered within 3 hours after symptom onset. Intracerebral thrombolysis by prourokinase is another choice if the middle cerebral artery is occluded and within less than 6 hours after onset. Although heparin especially medium dose is not proved to be effective, aspirin provides some benefit to patients with acute stroke. However, its effect is not fully satisfactory. Although numerous trials of neuroprotective drugs have reported disappointing results, thrombolytic and neuroprotective drugs will be used in combination. Free radical scavenger is one of the most promising agents among many neuroprotective agents.

Recently, new strategies to promote recovery of function has been paid much attention. These may include amphetamine-based therapeutics, enhancing neuritic outgrowth, enhancing proliferation of endogenous neural-lineage stem cells and transplantation of exogenously derived neural stem cells (36–39). These may change the treatment of acute ischemic stroke in the future.

**References**


