Information on treatment of Acute Ischemic Stroke with *t*issue *P*lasminogen *A*ctivator

What is a stroke?

A stroke is a problem with the tubes or vessels bringing blood to the brain, such that a part of the brain is injured. There are two main types of stroke, those associated with rupture of the blood vessels (hemorrhagic strokes) and those associated with the blockage of blood vessels (ischemic strokes).

What happens in an acute ischemic stroke?

In an acute ischemic stroke, the blood flow to a part of the brain interrupted because of sudden blockage of a blood vessel. The blockage is usually due to a blood clot and starves the brain of needed oxygen and nutrients. The center of the starved area may die quickly, and the surrounding area may die slowly over hours.

What is tissue plasminogen activator or tPA?

tPA is a medication that can dissolve blood clots. Because of its strong blood thinning action, bleeding into or around the brain can result as a side effect of its use. Bleeding can also occur in other parts of the body.

How can tPA help someone with an acute ischemic stroke?

tPA can sometimes dissolve the clot that is blocking the blood vessel and causing the ischemic stroke. If it does so, the blocked blood vessel reopens, allowing the previously starved brain to receive blood flow again with oxygen and nutrients. If the clot is dissolved soon enough, some or all of the brain may be rescued from the threatened injury. Rescuing brain that was starved may decrease the amount of disability that results from the ischemic stroke.

A research study demonstrated that, overall, patients given tPA within 3 hours of ischemic stroke onset had better outcomes 3 months later than patients not given any treatment.

Do all stroke patients get this treatment?

No. Specific criteria are used to identify those patients most likely to benefit and to avoid serious side effects. If a stroke patient does not fulfill all of these criteria, the risks of therapy are probably higher and the chance of benefiting probably lower - exactly how much is unknown. (see below)

What are the potential benefits?

The potential benefits are all related to an increased chance of having a good outcome, namely little or no disability remaining after recovery from the stroke. If stroke patients meet all the below criteria, their chances of having a good outcome increase from 29% without tPA to 41% with tPA (these percentages may vary somewhat depending on the severity of the stroke). Thus, even though the chances for a good outcome are improved, over half of the stroke patients who are given tPA will still have disability from their stroke. A good outcome is not guaranteed.

What are the potential risks?

The major risk of tPA therapy in stroke patients is that they will bleed into the injured area of the brain, causing a worsening of their condition and even death. The chance of serious bleeding into the stroke area is less than 0.6% in stroke patients not treated with tPA versus 6.4% in those who get tPA (this risk may be higher in patients with ***Cautionary Criteria*** as noted below). In other words, tPA increases about 10 times the chance of a bleed that worsened a patient's condition. About 20% of patients will die within 30 days of their stroke, regardless of tPA. Despite this increased risk of hemorrhage, overall patients are likely to benefit as described above.

What tests will be done?

No testing beyond what would be routine in a patient with stroke will need to be done. These standard tests include blood work and imaging, including a CT scan of the head to make sure no hemorrhage is present before proceeding with the tPA therapy. A repeat CT scan and further blood testing may be performed depending on how the patient responds to treatment.

If the patient has all of the below inclusion criteria and none of the exclusion criteria, he or she is eligible for treatment with t-PA.

INCLUSION CRITERIA

- Age 18 or greater (safety and efficacy for patients > 80 yoa is based only on observational, phase IV data, tPA should be used with caution in such cases)**.**

- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit with NIHSS $\geq$ 4
    - o defined as impairment of language, motor function, cognition, gaze, vision, neglect or some combination of these problems; isolated severe aphasia may present with NIHSS < 4 and still be worthy for consideration for IV tPA treatment.
    - o Ischemic stroke is defined as an event characterized by the sudden onset of an acute focal neurologic deficit presumed to be due to brain ischemia after CT ***excludes*** hemorrhage.

- Onset of symptoms of ischemic stroke within 3 hours of the time to initiation of treatment with intravenous tissue plasminogen activator (t-PA).

CAUTIONARY CRITERIA

(not absolute contraindications, often imply overall poorer prognosis, may increase risk of early symptomatic hemorrhage, yet do not exclude the possibility of benefit from tPA therapy)

- Age > 80 yoa (use is based only on observational, phase IV data, this should be pointed out during consent of such cases)**.**
- Severe stroke; including coma, severe obtundation, fixed eye deviation or complete hemiplegia, NIH Stroke Scale $\geq$ 20
- Evidence of early CT changes consistent with brain ischemia, such as loss of differentiation between gray and white matter, sulcal effacement, hypodensity or mass effect. Especially if > 1/3 of the MCA territory.
- Pregnancy; tPA has been given, with varying levels of success, risks to fetus and woman not clearly known, but may be considerable

EXCLUSION CRITERIA

- CT scan with evidence of hemorrhage.
- Patient has minor stroke symptoms (NIHSS < 4) or has major symptoms that are rapidly improving by the time of initiating treatment with t-PA.
- History of a stroke, myocardial infarction or head trauma within the previous 90 days.
- Paralysis that might be due to a known active seizure disorder or a first seizure within the 6 hours immediately prior to initiating treatment with t-PA.
- Previous known intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, arteriovenous malformation, or aneurysm.
- Clinical presentation suggestive of subarachnoid hemorrhage, even if initial CT scan is normal.
- Hypertension with systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg on repeated measures prior to study entry unresponsive to intravenous antihypertensives to reduce blood pressure to within these limits.
- Presumed septic embolus.
- Surgery or biopsy of parenchymal organ within the previous 14 days.
- Trauma with internal injuries or ulcerative wounds within the previous 30 days.

- Any active bleeding or acute trauma (fracture) on examination

- Gastrointestinal or urinary tract hemorrhage in previous 21 days.

- Known hereditary or acquired hemorrhagic diathesis
    - PTT or PT greater than normal;
    - unsupported coagulation factor deficiency;
    - oral anticoagulant therapy with prolonged PT (>15 sec or INR > 1.7);
    - use of heparin in previous 48 hours with a prolonged PTT;
    - use of any experimental antithrombotic agent or participation in such a trial (unless randomization is emergently broken and patient identified as having been on placebo).
    - [Note: use of ASA up until time of CVA was not an exclusion per NIH protocol, the effect of prior use of ticlopidine or clopidogrel has not studied thus is not a clear exclusion]

- Parturition within the previous 30 days.

- Baseline lab values:
    - glucose < 50 or > 400;
    - platelets < 100,000;
    - Hct < 25.

- Arterial puncture or venous puncture at non-compressible site in the last 7 days.

- Other serious, advanced, or terminal illness.

- Any other condition that the physician feels would pose a significant hazard to the patient if t-PA therapy were initiated.