Fibrinolysis and cerebral reperfusion: the role of TCCD

G. Malferrari
M. Zedde

Neurology Department, Stroke Unit, Santa Maria Nuova Hospital, Reggio Emilia, Italy
E-mail: Malferrari.Giovanni@asmn.re.it

Thrombolytic treatment: benefits and limits

Recombinant tissue plasminogen activator (rtPA) is approved in the USA for the treatment of selected patients with acute ischaemic stroke within 3 hours of symptom onset. In Europe, rtPA was approved *sub conditione* in 2002 pending the results of a phase IV monitoring study, designed in order to demonstrate that efficacy and safety shown in clinical trials can be replicated in clinical practice in centres inexperienced in thrombolytic treatment. NINDS trial results show that rtPA prevents one death or dependency each 7 treated patients. In order to monitor the effects of treatment and the potential complications, a stroke team and a stroke unit are needed.

The last Cochrane Library meta-analysis points out that thrombolytic therapy, administered within 6 hours of stroke, reduces death and dependency at 3 months. This effect seems to be present in spite of an increasing early and late fatality rate, mainly attributable to intracranial haemorrhage (ICH). But while rtPA use is associated with less damage and a greater benefit, "... the optimum criteria to identify the patients most likely to benefit, the latest time window, and the potential risk of prior aspirin use, increasing age, stroke severity, dose, and route of administration are not clear" (Davalos, 2005).

Analysis of pooled data from the ATLANTIS, ECASS and NINDS trials demonstrated that the sooner rtPA is administered, the greater the benefit will be (greatest if treatment is started within 90 min.). Moreover, the results suggested a potential benefit beyond 3 hours with a slightly significant advantage until 4.5 hours (as the recent ECASS III trial outlooked). Beyond this interval of time, treatment was associated with increased mortality (OR: 1.45; 95% CI: 1.02-2.07). The ICH rate is related to age and rtPA administration, but does not seem to be related either to interval between onset and treatment, or to stroke severity (NIHSS score). Therefore, the apparent reduction of benefit in the late time window does not seem to be the result of an increased ICH rate.

Data from open use in routine clinical practice, after rtPA approval, suggest that a low platelet count and increased blood glucose values are risk factors for a symptomatic ICH. High blood glucose values seem to be crucial for the outcome of thrombolysed patients. Several authors and datasets have shown that increased blood glucose is related to a neurological worsening, or lack of improvement. The benefits of recanalisation are abolished in patients with blood glucose > 140 mg/dl before treatment.

Conversely, there is no doubt that early hypodensity on CT predicts haemorrhagic transformation in patients treated with rtPA. Clinical trial findings show a 2-5 fold increase in symptomatic ICH risk.

The risk is marked mainly when early ischaemic signs occur in more than 1/3 of the MCA territory. The ASPECTS method, a system evaluating 10 different areas in two examination planes of unenhanced brain CT, demonstrated that a score ≤ 7 correlates with a high rate of symptomatic ICH (14%) and a lower rate of clinical recovery (5%). However, the ASPECTS system has not been validated prospectively and clinical trials found that, within 3 hours of symptom onset, the benefit of rtPA over placebo is significant even in patients with early signs of infarction. Although the uncertainty remains, the general recommendation is: do not treat patients with clear hypodensity of ≥ 1/3 of MCA territory.

Since 2003, rtPA has been widely used in Europe, even though the rate of treated patients is still low. Most treated patients were included and followed up in a prospective registry, designed to monitor the efficacy and safety of rtPA in comparison with randomised trial findings.

Currently around 3,000 patients from more than 230 centres have been registered in SITS-MOST. About half of these patients were treated in hospitals without previous experience in the use of rtPA. Overall mortality (13%) and independence (52%) at 3 months were similar to RCT data and the symptomatic ICH rate

was lower than in the RCTs (5%), suggesting that training is followed by a reduction of haemorrhagic complications. This training curve was serve in SITS-MOST and in other community multicentre studies. Protocol violations correlated with case fatality rate and mortality was higher in hospitals with limited experience (those with fewer than 5 treated patients per year).
Despite the wide use of rtPA in several countries, there are still several limitations, obstacles to the optimal management of thrombolytic treatment. For example, less than 4% of patients receive iv rt-PA treatment, systemic reperfusion is achieved in less than 40% of patients, symptomatic haemorrhagic complications are still high (5%), a complete functional recovery is achieved in 40% of patients, the treatment is denied to most patients (i.e., wake-up stroke), and there are no widely accepted alternatives for non-responders.
In addition to an increase in the number of patients submitted to thrombolytic treatment, extensive registries and new RCTs should answer the open questions on time window, dose, drug, administration route and patients who are more likely benefit and less likely to be damaged by treatment.
Less than 4-8% of patients receive iv rtPA in dedicated centres. Emergency management, early neurological evaluation and a neuroimaging study are crucial for the administration of treatment within 3 hours. In several countries, even though up to 30% of patients reach hospital within 3 hours of symptom onset, only a small proportion is actually treated. The need for strict adherence to protocol precludes treatment in 1/5 of selected patients, while 1/3 are excluded for a mild stroke or rapidly improving symptoms before treatment, and 1/4 for avoidable reasons, such as late evaluation or clinical doubts. The extension of the time window to 6 hours would have little effect on treatment rate (8.3%). Less restrictive criteria for thrombolysis could increase the eligibility for rtPA (currently estimated at 29% of all ischemic strokes), for example, if time was not an exclusion criterion. The EMEA regulatory exclusion criteria are not accepted by many experts; in particular, the under-80-years age restriction, and anticoagulant treatment with INR ≤ 1.5.
In the near future, a series of potential interventions, such as sonothrombolysis and ia thrombolysis, could increase the recanalisation rate. Indeed, ultrasound-enhanced systemic thrombolysis produced an absolute increase of 20% in MCA recanalisation rate, according to the CLOTBUST study results. Recently, transcranial ultrasound was shown to accelerate clot dissolution in some patients with contraindications for rtPA, although these preliminary data need to be confirmed in a wider trial. In a recent meta-analysis it was shown that ia thrombolysis is efficient until 6 hours after symptom onset in MCA occlusions and another recent meta-analysis suggested that ia thrombolysis could significantly increase (2.3 times) the probability of a favourable outcome. Symptomatic ICH increases 3.4 times, but the overall risk of death is reduced by 40%. No randomised controlled trial has compared ia and iv thrombolysis in acute ischaemic stroke. Although some indirect data suggest a higher recanalisation rate for ia treatment, it is not clear whether the longer time needed for the procedure counteracts its potential benefit. The results of EMS and IMS multicentre trials and those of a single-centre study of combined iv+ia rtPA, were compared to NINDS results in patients younger than 80 years and with NIHSS score 6-10 treated with iv rtPA within 3 hours. Although combined treatment is safe, the frequency of a favourable outcome seemed to be similar to that of iv rtPA in the NINDS trial.

Evidence of arterial occlusion before rtPA administration in acute stroke

The rationale for using thrombolysis in acute ischaemic stroke is to obtain recanalisation of occluded arteries in order to restore brain function, saving tissue at risk. This procedure is based on the knowledge that most ischaemic strokes are caused by acute arterial occlusions, due to emboli or clots. Indeed, histological and angiographic studies demonstrated the presence of an occluding clot in up to 80% of ischaemic strokes, while in the other 20% without angiographic evidence of occlusion it was not possible to exclude an early occlusive event with spontaneous recanalisation before vascular imaging, or thrombus fragmentation in the distal circulation. The speed of angiographic lysis of intracranial thrombus seems to be strongly correlated with early neurological improvement, reduced infarction size and better outcome.

"Vascular imaging is unnecessary prior to thrombolytic therapy"

The need to obtain vascular imaging data before thrombolysis is the subject of a controversial debate. It is suggested by several experts that, if possible, every effort should be made to demonstrate a large artery intracranial occlusion (by means of the modern neuroimaging techniques) before rtPA administration. The main argument advanced by those who support this idea is that thrombolytic treatment could otherwise be administered without real requirement in some patients, given that the current recommendations favour the speed over the specificity of treatment. This assertion, attractive from the physiopathological point of view,

still has to be demonstrated. However, an independent committee that re-analysed NINDS original data could not identify any subgroup of acute ischaemic stroke patients who benefit more or less from thrombolysis. The original study (1995) showed a benefit even in patients with infarction related to "small vessel disease". Such patients would probably not have presented a vessel occlusion on MRA or DSA and therefore would not have been candidates for treatment. Maybe it can be argued that a less well-known subgroup of lacunar infarction is due to parent artery disease co-involving the perforator ostium, and that ultimately this subgroup is part of large artery disease.

Those against a more selective vascular approach affirm that in the management of acute stroke patients there is no effective alternative to rtPA and that it is unlikely that more suitable selection of patients for thrombolysis (using the NINDS protocol) would add benefit. Moreover, extensive clinical trials have failed to provide definite evidence of the existence of any subgroup of acute stroke patients in whom the risk and consequences of having a symptomatic ICH would outweigh the potential benefits of rtPA administration. Thus, "...the clinician's goal should be to identify those patients who fulfill the criteria outlined in the original protocol as fast as possible. Additional vascular examinations cost precious time, and there is no data justifying subgroup selection beforehand" (Szabo, 2006).

Accordingly, since treatment should nevertheless be given as soon as possible in order to maximise benefits and facilitate vascular imaging, and given that for most patients enrolled in the classical trials on iv thrombolysis no information is available on the real presence and site of an arterial occlusion before starting treatment, as well as the fact that the meta-analysis of the previously cited studies reported an overall benefit from rtPA administration within 3 hours of symptom onset irrespective of subtype (e.g., lacunar or large vessel disease), it is currently not considered mandatory to evaluate the presence and site of an arterial occlusion before making a decision on thrombolytic treatment; it is simply advised in the guidelines of some scientific societies.

It is, however, correct to remark that what for the abovementioned authors is not mandatory for the treatment decision becomes more than advisable in the follow up of recanalisation during and after rtPA administration. This is because some techniques, like neurosonology, have demonstrated their ability to achieve findings that reliably predict prognosis and need for further treatment: "… regular Doppler or duplex examinations should be performed in order to estimate recanalization of intracranial pathology. Transcranial color-coded duplex sonography enables a reliable assessment of intracranial stenoses and is an ideal bedside technique for follow-up evaluations" (Szabo, 2006).

A technically correct brain CT should be mandatory before thrombolysis in order to exclude haemorrhage and non-ischaemic diagnoses, as well as to visualise early infarction signs. In the NINDS trial, pre-treatment brain CT was used only to exclude a haemorrhage, and the identification of early infarction signs was not an exclusion criterion for enrolling patients. Early ischaemic signs were present in 31% of basal examinations, although there was no relation to the development of symptomatic ICH after adjusting for NIHSS score ($p>0.22$). Instead, the presence of major ischaemic changes on basal brain CT, defined as a substantial mass effect or the visualisation of a hypodensity involving more than 1/3 of the MCA territory, is associated with a poor outcome, independently of treatment, and with an increased ICH risk following thrombolysis (OR, 7.8; 95% CI, 2.2-27.1).

Persuasive confirmation in the real world of trial results comes from open rtPA studies, recently reviewed, whose data demonstrate that rtPA administration within 3 hours of symptom onset leads to rates of mortality, symptomatic haemorrhagic transformation (fatal or not) and good clinical outcome similar to those recorded in the randomised trials. Moreover, protocol violations (treatment beyond 3 hours, antithrombotic drug administration within 24 hours of thrombolysis, high arterial pressure, abnormal clotting times at the time of treatment) are significantly related to symptomatic haemorrhagic transformation.

Therefore, Canadian and European guidelines recommend that iv thrombolysis be used only by physicians with documented experience in diagnosis and management of stroke, who work in centres with specifically approved treatment protocols.

Vascular occlusion in the acute phase and prognosis

With iv thrombolysis, in the best conceivable scenario, early complete recanalisation is achieved in only 30%-40% of patients and less than 50% of treated subjects become long-term independent. Several factors can bias the response, in terms of recanalisation, to iv thrombolysis (time-to-treatment, size and site of arterial occlusion, stroke subtype). Information on early predictors of resistance to recanalisation can be useful for selecting patients for more aggressive reperfusion strategies. Starting from Caplan's assumption that "…ideally the treatment of a patient with cerebral ischaemia should be guided by knowledge of the na-

ture, localization and severity of the occlusive disease within the extracranial and intracranial vessels", it is possible to find literature evidence dating back some years on different responses to thrombolysis according to the vascular occlusion site. As early as the NINDS study, it was pointed out that patients with contemporary occlusion of the ICA and MCA gained less benefit from thrombolysis than ones with MCA occlusion alone, mainly in its distal segment, even though the clinical presentation was the same in the two subgroups. Del Zoppo and co-workers, in a series of 139 patients with ischaemic stroke, treated with thrombolysis, found greater difficulty of reperfusion in cases of contemporary occlusion of the ICA and MCA than in cases of MCA occlusion alone.

Finally, several studies demonstrated poor revascularisation in cases of T occlusion, treated with iv or ia rt-PA. Therefore, there are several stroke subtypes and several intracranial occlusive patterns with different response to thrombolysis. Alexandrov in a recent work wrote: "…the patients presented with similar severity of hemiplegia, but the severity of perfusion deficit and recovery were dramatically different. TCD allows early differentation of patency and natural history of MCA thromboembolic events. This may have important implications in the decision for thrombolytic therapy…".

Moreover, in the presence of similar stroke severity, patients with tandem occlusion of extracranial ICA and MCA have a lower recanalisation rate and a poorer outcome than those with MCA occlusion alone. Tandem or T occlusion is not an infrequent finding. Indeed recent studies show that about 1/4 of MCA occlusion patients have a simultaneous ICA occlusion and up to 50% of patients with ICA occlusion have a proximal MCA occlusion. In patients with tandem occlusions of the ICA/MCA, clinical presentation and neurological severity are similar to what is found in those with MCA occlusion alone.

Patients with tandem ICA/MCA occlusion have a better outcome if MCA recanalisation occurs early, regardless of the persistence, or otherwise, of the ICA occlusion. However, there are no certain data on rates of early recanalisation of MCA occlusion in tandem occlusion. A retrospective analysis of the CLOTBUST database was conducted in order to evaluate MCA recanalisation and clinical outcome in patients treated with iv rtPA for tandem ICA/MCA occlusions and isolated MCA occlusion.

The results of this study show that early complete recanalisation and early neurological improvement are more common in the subgroup with isolated MCA occlusion than in the one with tandem lesions but similar basal features. MCA recanalisation rates were also lower with tandem lesions than with isolated lesions, confirming data from other studies at 24 hours from symptom onset. In particular, the isolated lesion subgroup had, during the first 2 hours, a higher early complete recanalisation rate than the subgroup with tandem occlusion. Recanalisation rate increased over time in the isolated lesion subgroup, but not in the one with tandem lesions. Recanalisation was less frequent in the "large artery disease" stroke subtype than in the cardioembolic one. It is also possible that these patients had a greater chance of achieving complete recanalisation because of monitoring with TCD during the first 2 hours. A direct comparison with previous data is not possible, because this is the first study reporting early recanalisation rates.

The low MCA recanalisation rate recorded in the subgroup with tandem occlusion may be ascribed to the large clot burden if ICA is occluded, but also to the fact that ICA lesions may produce hypoperfusion and reduce release of rtPA to the MCA thrombus.

In the context of tandem lesions, intracranial occlusion site may be not only a surrogate of thrombotic burden but also reflect several haemodynamic conditions and exposure to the thrombolytic drugs, which can modify response to iv thrombolysis. The authors thus hypothesise that relative resistance to thrombolysis in patients with tandem occlusion changes according to MCA clot location. Indeed, tandem occlusion independently predicts a poor response to thrombolysis in patients with proximal occlusion but not in those with distal occlusion; the latter show a recanalisation rate similar to that of patients with distal MCA occlusion alone.

Therefore, tandem occlusion may represent the worst scenario for standard thrombolysis in terms of recanalistion rate and outcome.

References

1. Malferrari G, Zedde M, Marcello N. Role of ultrasound vascular imaging in the acute phase of stroke. Vascular Disease Prevention 2008;5:252-269
2. Wahlgren N, Ahmed N, Dávalos A et al.; SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-282
3. Wardlaw JM. Overview of Cochrane thrombolysis meta-analysis. Neurology 2001;57(5 Suppl 2):S69-S76
4. Wunderlich MT, Goertler M, Postert T; Duplex Sonography in Acute Stroke (DIAS) Study Group and the Competence Network Stroke. Recanalization after intravenous thrombolysis: does a recanalization time window exist? Neurology 2007;68:1364-1368