Intra-Arterial Fibrinolysis for Acute Ischemic Stroke
The Message of Melt

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For nearly a decade, intra-arterial fibrinolytic therapy for acute ischemic stroke has stood poised on the threshold of a definitive evidential basis and widespread acceptance. The positive result of the phase 3 PROACT II trial in 1999 appeared to validate the pathophysiologically eminently reasonable strategy of endovascular recanalization in acute ischemic stroke. Endovascular therapy delivers lytic agent at high concentration directly to the clot, increasing lysis rates compared with intravenous therapy, while minimizing systemic exposure and extracerebral bleeding complications. Leading stroke centers adopted endovascular recanalization therapies as a common off-label treatment option for patients beyond the 3-hour window.

However, proponents of evidence-based medicine noted that a single, small phase 3 clinical trial was insufficient to provide definitive proof of efficacy. The US Food and Drug Administration and international regulatory agencies did not approve a stroke label for pro-urokinase. The expense of a confirmatory phase 3 trial of pro-urokinase proved daunting to pharma and none was undertaken. In US national practice guidelines, intra-arterial fibrinolysis occupied a gray zone, receiving a Level B recommendation, indicating the incomplete foundation of a single dose-ranging and single positive phase 3 trial. The limitations of this evidential base have prevented regional emergency medical systems from organizing delivery of patients directly to endovascular hospitals.

The results of the MELT trial, reported in this issue of Stroke, are therefore very welcome, providing additional information regarding intra-arterial fibrinolytic therapy that complements and supports previous studies. Taking advantage of the delay until October 2005 of regulatory approval in Japan of intravenous tissue plasminogen activator in the under 3-hour window as a stroke therapy, the MELT trialists performed a trial of intra-arterial urokinase among under 6-hour patients, including many early arriving patients. The study design largely paralleled PROACT II, enrolling only patients with M1 or M2 middle cerebral artery occlusions, and use of concomitant antithrombotics was prohibited in the treated group for the first 24 hours after therapy.

However, there were potentially important differences between PROACT II and MELT in implementation of the interventional procedure. In PROACT II, interventionalists positioned the microcatheter in the proximal third of the target clot and infused lytic agent directly into the thrombus, whereas in MELT interventionalists passed the microcatheter through the entire clot and infused the lytic agent beyond the distal face of the thrombus. In PROACT II, the lytic agent was administered by slow drip continuously over 2 hours and the entire dose given whether or not complete lysis was achieved before the end of infusion. In MELT, the lytic agent was administered by repeated boluses and the infusion discontinued early if complete recanalization had been achieved. In PROACT II, concomitant mechanical disruption of the clot was not permitted, whereas in MELT interventionalists were permitted to mechanically disrupt the thrombus with a guide wire and did so in more than two-thirds of cases.

The patient populations enrolled in PROACT II and MELT were fairly comparable in age and gender, but differed in several important respects. MELT patients had substantially less severe neurological deficits at entry (National Institute of Health Stroke Scale 14 versus 17), less often harbored early infarct signs on CT (47% versus 76%), and were randomized earlier (3.3 versus 4.9 hours). Start of intra-arterial therapy in the treatment group occurred 1.5 hours sooner in MELT than in PROACT II (3.8 versus 5.3 hours). As would be expected with a study population of lesser stroke severity clinically and radiologically, the MELT control group fared better than the PROACT II control group, (nondisabled final modified Rankin Scale [mRS] score 0 to 2 outcomes achieved by 39% versus 25%) affording less of a chance for treatment to show a benefit.

The technical efficacy of intra-arterial urokinase in reopening target arteries in MELT was moderate. Partial or complete recanalization was achieved in a high proportion of subjects, 74%, comparable to the 66% rate achieved by pro-urokinase in PROACT II. However, the low rate of complete recanalization (5% in MELT, even lower than the 18% in the treated arm of PROACT II) reconfirms that intra-arterial fibrinolytic therapy alone is not a definitive solution to the challenge of rapidly and fully recanalizing occluded cerebral arteries.

The definition of symptomatic intracranial hemorrhage in MELT differed from PROACT II and indeed from all prior fibrinolytic trials, making safety comparisons provisional. Symptomatic hemorrhage was defined as any CT evident hemorrhage associated with a 4-point change in the National Institute of Health Stroke Scale or the presence of any new “objective sign”. The definition of, and process for adjudicating, new “objective signs” is not well delineated in the
MELT report. However, the rate of symptomatic hemorrhage appears roughly comparable with intra-arterial urokinase (9% at 24 hours) as with intra-arterial pro-urokinase (10% at 24 hours).

With regard to clinical outcome, MELT presents us with a tantalizing result. The study was formally nonpositive on its prespecified primary end point of the proportion of patients with nondisabled outcome (mRS ≤2) at 3 months, with an absolute increase of 10.5%. However, for the prespecified secondary end point of the proportion of patients with excellent outcome (mRS ≤1) at 3 months, the treatment group was superior to the control group (absolute increase of 19.3%) at a conventional level of statistical significance, albeit unadjusted for multiple comparisons.

The phenomenon of recanalization trials being positive on some but not all end points has occurred before, and we have recently come to better understand the determinants and import of positivity on different end points. When recanalization therapies are given early to patients, within the first 3 hours, responders will frequently achieve excellent outcomes and, in dichotomized analyses, an extreme good outcome threshold (mRS ≤1) will often be more sensitive in detecting a treatment effect than a moderately good outcome threshold (mRS ≤2), as in the 2 NINDS tPA trials. When therapies are given late, beyond the 3-hour window, after some damage has already accumulated in most patients, excellent outcomes cannot be frequently achieved, and moderately good outcome thresholds will often be more sensitive in detecting a treatment effect than extreme good outcomes, as in ECASS 2 and PROACT II. In MELT, the greater positive result on the extremely good than moderately good outcome measure is exactly what would be expected in a trial that enrolled relatively mildly affected stroke patients and treated them in an early time frame.

An updated meta-analysis of intra-arterial fibrinolysis trials incorporating MELT is shown in the Figure. Stopped early because of external considerations, MELT was underpowered and formally negative, and must be interpreted with caution. However, the MELT trialists deserve our gratitude for reporting a trial that contributes to the cumulative evidence of benefit of intra-arterial fibrinolytic therapy in acute ischemic.

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### References

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