Management of severe Stroke
Thrombolyis-Hemicraniectomy-Hypothermia

Lecture delivered at occasion of the Mihara Award Celebration

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Thrombolytic therapy with rtPA (0.9 mg/kg body weight, maximum dose 90 mg) given within 3 h after stroke onset significantly improves outcome in patients with acute ischaemic stroke: the number needed to treat (NNT) to achieve a favourable clinical outcome after 3 months is 7. By contrast, the ECASS (European Cooperative Acute Stroke Study) and ECASS II studies, both with impressive trends towards improved outcome, did not show statistically significant superiority of rtPA for the primary endpoints when treatment was given within 6 h. Trials with rtPA, involving a total of 2,889 patients, have shown a significant reduction in the number of patients with death or dependency (OR 0.83; 95% CI 0.73-0.94). A pooled analysis of individual data of rtPA trials showed that, even within a 3-hour window, earlier treatment results in a better outcome (0-90 min: OR 2.11; 95% CI 1.33-3.55; 90-180 min: OR 1.69; 95% CI 1.09-2.62). This analysis suggested a benefit up to 4.5 h.
Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise and brain CT is assessed by an experienced physician. Whenever possible, the risks and benefits of rtPA should be discussed with the patient and family before treatment is initiated.
The recently published trial European Cooperative Acute Stroke Study III (ECASS III) has shown that intravenous alteplase administered between 3 and 4.5 hours (median 3 h 59 min) after the onset of symptoms significantly improves clinical outcomes in patients with acute ischemic stroke compared to placebo. The absolute improvement was 7.2% and the adjusted OR of favorable outcome (mRS 0-1) was 1.42, 1.02-1.98. Mortality did not differ significantly (7.7% versus 8.4%), but alteplase increased the risk of SICH (2.4% vs 0.2%). Treatment benefit is time-dependent. The number needed to treat to get one more favourable outcome drops from two during the first 90 minutes through seven within 3 hours and towards 14 between 3 and 4.5 hours.

The SITS investigators compared 664 patients with ischaemic stroke treated between 3 and 4.5 hours otherwise compliant with the European summary of the product

characteristics criteria with 11 865 patients treated within 3 hours.
In the 3-4.5-hour cohort, treatment was started on average 55 minutes later after symptom onset. There were no significant differences between the 3-4.5-hour cohort and the 3-hour cohort for any outcome measures, confirming that alteplase remains safe when given between 3 and 4.5 hours after the onset of symptoms in ischaemic stroke patients who otherwise fulfil the European summary of product characteristics criteria.

European regulatory agencies do not advocate rtPA treatment in patients with severe stroke (NIHSSS >25), extended early ischaemic changes on CT-scan, or age above 80 years (unlike the US labelling). However, the NINDS (National Institute of Neurological Disorders and Stroke) Study showed that the extent of early ischaemic changes (using the ASPECT score) had no effect on treatment response within the 3-hour time window. Moreover, observational studies suggest that rtPA given within 3 h of stroke onset is safe and effective in patients over 80 years of age [389–391], but more randomized data are pending.

While thrombolysis in an early time window up to three hours, and more recently up to 4 ½ hours is the approved treatment in the early phase of acute stroke, several problems remain, when it comes to the development of large, live-threatening stroke.

Over the past 15 years, two modalities have been developed to cope with the syndrome of malignant MCA infarction.

The first one is the decompressive surgery. From case series over prospective registries it appeared that early decompressive surgery, that is within 36 to 48 hours is live saving. However, there was always the concern that saving lives could be associated with a very high range of patient surviving in a very bad functional state e.g. a modified Rankin of 5.

Although the condition is not frequent several groups have encountered the task of performing randomized trials to establish the functional benefit of decompressive surgery. All singular trials had very slow recruitment and it was the novel approach of analysing combined data from several unpublished trials that finally let to a convincing result regarding functional outcome: decrompressive surgery is not only live saving, it also helps survival in a decent and sometimes very good clinical state.

The other method that has been tested in case series and small prospective cohort studies is hypothermia. However, in contrast to decompressive surgery, no randomized trials have yet been performed. Many producers of cooling devices were only interested in showing feasibility and practicability regarding cooling down the body temperature, but never looked at functional outcome.

From animal experiments, many people believe that hypothermia a probably the strongest neuroprotective measure that can be used. Studies in patients after circulatory or rest have shown that the outcome in those patients cooled down for 24 hours is much better. However, for the stroke indication these studies are still outstanding. We know of several groups around the world, who would love to approach this topic in a scientific rigorous way. Therefore with the Mihara Award I will try to set the basis for the design of a multicenter large scale individual funding prospective trial series that will alternately test the value of hypothermia in acute ischemic stroke.