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A CRITICAL ASSESSMENT OF EDARAVONE ACUTE ISCHEMIC STROKE EFFICACY TRIALS: IS EDARAVONE AN EFFECTIVE NEUROPROTECTIVE THERAPY?

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Abstract

Importance of the field—Edaravone (Radicut®) is a free radical scavenger marketed in Japan by Mitsubishi Tanabe Pharma Corporation to treat acute ischemic stroke (AIS) patients presenting within 24 hours of the attack. Injectable edaravone ampoules (30mg b.i.d, i.v., 14 days) were first approved on May 23, 2001. On January 19th 2010, as a new innovation, the Radicut BAG was approved by the Japanese Ministry of Health and Welfare. Efficacy of edaravone range from large significant clinical improvements to only modest improvements in clinical function measured using standard stroke scales when administered 6–72 hours following an ischemic stroke. With almost 17 years of edaravone clinical experience, a few adverse events including acute renal failure have been noted.

What the reader will gain—This is the only article to date to critically review available clinical efficacy and toxicology data published in the literature to ascertain whether edaravone should be further pursued as a candidate for development worldwide.

Areas covered in this review—This review covers clinical studies done during the periods 1993–2008.

Take home message—Edaravone may a useful neuroprotective agent to treat more than 15 million worldwide victims devastated by stroke annually. Additional clinical studies are necessary to verify the efficacy of edaravone.

Keywords

neuroprotection; embolism; acute ischemic stroke; clinical; behavior; toxicity; translational science; antioxidant; Radicut; thrombolytic

1. Background

1.1 AIS Incidence

AIS is the third leading cause of death and the leading cause of adult disability in the USA[1] with an estimated cost of \$68.9 billion. Annually, approximately 795,000 people suffer a stroke (one every 40 seconds with 1 mortality every 3 minutes), 75% of which are first strokes and the remainder recurrent attacks [2]. The World Health Organization (WHO) estimates that 15

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million people suffer strokes worldwide annually and more than 5 million stroke victims die from the brain insult and 5 million are permanently disabled[3] and require medical care.

1.2 AIS subtypes defined

According to the National Institutes of Neurological Disorders and Stroke (NINDS) classification of stroke types and population-based research studies[4,5], AIS can be classified as the following: (1) cardioembolic stroke (29% of cases), in which the embolism arises from a cardiac source; (2) atheroembolic stroke (16% of cases), which can be associated with narrowing of a cervicocephalic artery; and (3) small vessel lacunar stroke (16% of cases), which are defined as pure motor, sensorimotor or sensory strokes, in addition to ataxic hemiparesis and result from thrombosis in one of the deep penetrating branches from larger cerebral arteries. The majority of strokes (39%) do not have a known cause.

2. Current Treatment: Tissue Plasminogen Activator (tPA, Alteplase®, Activase®, Actilyse®)

The only FDA approved treatment for AIS is the thrombolytic, tissue plasminogen activator (tPA, Alteplase), a plasminogen activator that promotes thrombolysis by activating the endogenous fibrinolytic system[6–9]. In brief, tPA catalyzes the conversion of plasminogen to plasmin, which in turn degrades fibrin and leads to clot lysis and cerebral reperfusion. Alteplase has been shown to be effective up to 4.5 hours after a stroke[10,11], but is currently only Food & Drug Administration (FDA) approved for use within the first 3 hours of a stroke in patients documenting the absence of an intracerebral hemorrhage (ICH). In alteplase-treated patients, the short-term incidence of symptomatic ICH is significantly higher in tPA-treated patients than in placebo-treated controls [12]. Following the initial approval of alteplase treatment, the treatment was further developed and refined to a point where in the most recent ECASS III trial [10] the investigators showed that tPA could be administered up to 4.5 hours following a stroke without an increased incidence of mortality. The trial showed that the incidence of ICH and sICH was higher with alteplase than with placebo (27.0% vs. 17.6%; $P=0.001$ and 2.4% vs. 0.2%; $P=0.008$), respectively. However, the mortality rate did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; $P=0.68$) and there was no significant difference in the rate of other serious adverse events (SAEs)[12]. Clearly, this is a major advancement in the stroke field; however, with only one effective FDA-approved stroke treatment there remains a need to develop treatments for stroke.

3. Free Radicals as a Target

Free radicals are a valid target for therapeutic intervention for the treatment of AIS [13–15], because oxidative stress is a major component of the ischemic stroke cascade [15–17], which is activated following vascular occlusion. However, the ischemic stroke cascade is a multi-component cascade with sequential activation of a complex series of pathophysiological events that evolve temporally [14,15]. The key to developing clinically effective molecules may lie in the ability of compounds to inhibit multiple ischemic cascade pathways or physiological simultaneously or sequentially! Does edaravone fit the profile of a multi-target drug? Yes, based upon the following evidence.

3.1 Mechanism-Based Translational Research

Edaravone is a low molecular weight lipophilic (i.e. hydrophobic) free radical scavenger that readily crosses the blood brain barrier (BBB) [18,19]. The anti-oxidant activity of edaravone is its main proposed mechanism of action and an important one, since free radicals may cause injuries following a stroke[16,20–25]. The oxidative stress that occurs after an ischemic stroke produces reactive oxygen species (ROS) like hydrogen peroxide (H_2O_2), hydroxyl radical

(HO•) and superoxide anion radical ($O_2^{\bullet-}$) that bring about membrane lipid peroxidation and vascular compartment endothelial cell injury [18,19,24–26]. The primary focus of edaravone research has revolved around its potential to scavenge hydroxyl, peroxy and superoxide radicals that mediate neuronal and vascular damage [27–30].

Under physiological conditions with neutral or physiological pH, edaravone is present in an anionic form. Due to an electron transfer process, electrons released from the edaravone anion can scavenge radical species containing a free electron, such as a lipid peroxy radical (OOL•), which is formed after the free radical extraction of a proton from an unsaturated fatty acid. The transfer of electrons from edaravone (E) to a reactive oxygen species produces an edaravone radical (E•). Subsequently, the edaravone radical (E•) forms a peroxy radical of edaravone (E••OO), which incorporates the O species to form a 4,5-dione (i.e. 3-methyl-1-phenyl-2-pyrazolin-4,5-dione) and eventually 2-oxo-3-(phenylhydrazone)-butanoic acid (OPB). Details emphasizing the chemical process involved in the antioxidant mechanism of edaravone have been published [19,31,32].

However, the therapeutic benefit of edaravone may be due to more than its antioxidant activity and may be directly related to its multi-target pharmacology and the ability of edaravone to regulate numerous signaling pathways. For example, recent mechanistic research has suggested that edaravone can suppress delayed neuronal death [26,31,33–35], counteract microglia-induced neurotoxicity [29] and reduce the long-term inflammation [36]. It has also been shown that edaravone can inhibit lipoxygenase, an enzyme responsible for lipid oxidation damage [31] and could also directly suppress the oxidation of low-density lipoprotein [32]. In addition to the attenuating the deleterious effects mediated by the ischemic cascade, it has been suggested that may prevent the development of edema following a stroke by inhibiting astrocyte production of expression of vascular endothelial growth factor [37]. Moreover, Kituchi et al. [38] hypothesized that edaravone may reduce aquaporin-4 levels following an ischemic event, thereby reducing edema. Last, Yagi et al. showed that edaravone may reduce the activity of matrix metalloproteinase-9, and further protect against vascular damage and intracerebral hemorrhage (ICH) [39–41]. Taken together, edaravone may prevent neuronal degeneration, vascular compartment damage and behavioral deficits resulting from both ischemia progression and edema. Thus, edaravone may fit into a class of multi-target compounds that may be useful to treat stroke. Is this borne out by preclinical and clinical stroke studies?

3.2 Preclinical Translational Research

3.2.1 Rodent Studies—The first peer-reviewed rodent stroke study with edaravone was published in 1989 by Oishi and colleagues [42]. While the authors did not show any behavioral improvement or cell survival, they showed that edaravone attenuated polyvinyl acetate (PVA)-induced changes in brain monoamine metabolism [42] and suggested that edaravone was acting as a free radical scavenger to counteract the effects of PVA-induced ischemia. Nishi et al also used the PVA model and showed that edaravone prevented ischemia-induced edema [43]. These 2 seminal studies sparked the development and subsequent approval of edaravone for the treatment of AIS in Japan.

Following the early PVA studies, additional stroke studies were done using accepted rodent stroke models. For example, Jin et al. [44] used a standard ischemia model in gerbils to show that edaravone could increase cerebral blood flow following ischemia and reduce edema, but there was no significant effect of neuronal survival or mortality rate compared to the control group. In an intraluminal stroke model, Nito et al. [45] also showed that edaravone reduced edema. Watanabe from Mitsubishi Kasei Corp., the developers of edaravone published a report [46] showing that pre-treatment with edaravone (3 mg/kg i.v.) prolonged survival time in rats subjected to global ischemia and reduced BBB dysfunction, while post-treatment decreased

cortical infarct size, an effect that was postulated to be associated with edaravone-induced inhibition of iron-dependent peroxidation of mitochondrial membranes. In a rodent ischemia/reperfusion model, Wu et al [47] provided additional evidence that edaravone could reduce ischemia-induced infarct size. There have been numerous other rodent studies showing similar effects when edaravone is given either as a pre-treatment or post-treatment. Since they have recently been reviewed in detail, please refer to the original review articles [18,27,48–51]. However, important information regarding therapeutic window analyses in preclinical models, which are recommended by STAIR[52] and thereafter by Lapchak[13], have not been reported for rodents.

3.2.2 Rabbit Studies—The only available translational study used the rabbit small clot embolic stroke model (RSCM), which is a useful model and possibly a predictor of treatments that may show efficacy in human clinical trials[13]. The RSCM was the preclinical animal model used in the development and FDA approval of tPA, the development profile which has recently been reviewed in detail by Lapchak[13], but see[53–57] for the original publications. The RSCM uses embolization to cause multifocal cerebral ischemia, which results in graded behavioral deficits that can be quantified quantitatively [13,58–60]. The primary behavioral endpoint is based upon motor function components of the NIHSS scale [61–64]. In the RSCM, edaravone administered subcutaneously decreased behavioral deficits when up to 3 hours post-embolization [59]. Moreover, the study showed that edaravone could be administered in combination with standard dose intravenous tPA therapy, but the combination using maximally effective doses of both drugs did not result in either a synergistic or additive effect, most likely due to the achievement of maximal benefit by each drug as monotherapy[59]. Nevertheless, the study indicates that had a therapeutic window of at least 3 hours in rabbits. In a recent hypothesis driven translational research publication by Lapchak[13], a 3hour therapeutic window in the RSCM was calculated to represent approximately 7.3–9 hours in AIS patients. Is Edaravone effective in AIS patients within that projected therapeutic window? The following section will address the efficacy and therapeutic window data documented by clinical researchers in Japan and India.

3.3 Clinical Research Efficacy

3.3.1 Thrombotic/Embolic Strokes—The original 2003 *Otomo* clinical trial report from the Edaravone Acute Ischemic Stroke Group[65] is the only randomized, placebo-controlled, double-blind multicenter study using a 14 day treatment regimen. As shown in Table 1, the study was conducted between December 1993 and March 1996 and Mitsubishi Pharma Corp both supplied the test drugs and supported the studies. The dose used in the Otomo study[66] was cited to be based upon early phase 2 dose-finding and efficacy studies[66,67], which used doses from 10–60 mg b.i.d. In all patients entered into the trial, with mean time to treatment of 35.2 ± 26.6 hours and 37.3 ± 22.6 hours for placebo and edaravone respectively, a significant difference using the Wilcoxon's 2-tailed rank sum test between edaravone-treated and placebo-treated groups measured using the mRS ($p=0.0382$) was reported (Table 1). In addition, Figure 1 presents the primary clinical score data from the study when patients received edaravone within 24 hours of stroke onset. The subset analysis data clearly shows a significant ($p=0.0001$) shift in the proportion of patients with mRS scores of 0 and 1 following edaravone treatment and this was true when all study patients were assessed either 3, 6 or 12 months after stroke onset[65]. Clearly in this trial, edaravone produced significant clinical improvement in all patients receiving the drug, independent of the time to treatment time interval (i.e.: ≤ 24 , 25–48 or 48–72hours), however, the most pronounced effect was in the ≤ 24 hours group. It should be noted that in this trial, the majority of patients in each group were identified as thrombotic strokes (78–81%) with 17–19% being embolic strokes.

The *Inatomi*[68] retrospective historically-controlled study was differentiated from the Otomo trial[65] because the authors limited analysis to patients with embolic strokes. This study showed that edaravone treatment for 7 days could only produce a modest clinical improvement in AIS patients with NIHSS ≤ 7 upon entry into the trial (Table 2); efficacy that was not seen in the moderate to severe AIS patients (NIHSS >7) patients. Specifically, the data shows that edaravone-treated patients in the NIHSS ≤ 7 improved by 2 points whereas the control group became worse by 2 points. Moreover, the authors report that 6 months after AIS onset, patients who became independent (mRS <2) were more likely to have received edaravone than placebo, (41% versus 28%; $p=0.066$). Thus, the reports suggest that edaravone may only have utility in AIS patients with NIHSS ≤ 7 .

3.3.2 Lacunar Strokes—The *Mishina*[69] report is a small retrospective analysis study that included both control and edaravone-treated patients. This study, unlike the 2 previous studies described above, this study only included patients with identified lacunar infarctions using previously published criteria[70]. There was stratification of time to treatment for patients: ≤ 6 and 12–24 hours. Three month mRS rating scores were used as primary clinical criteria and an mRS score for improvement of ≤ 2 was defined as a good outcome. Final analysis only included 21 patients in the edaravone group compared to 49 patients in the control group (Table 2). Using a backward stepwise logistic regression analysis the authors concluded that there was a significant odds ratio effect in patients with edaravone treatment ($p=0.035$) that was also correlated with NIHSS ≤ 8 , but not time to treatment. The effect appears to confirm that reported by Otomo and suggests that only patient with mild strokes may benefit from edaravone treatment.

Using a separate lacunar stroke patient population, *Ohta*[71] also retrospectively studied the effects of edaravone on functional outcome. A significant difference to note in this study is an acute time to treatment of 9.8 ± 7.0 and 9.2 ± 5.8 hours in the control and edaravone-treated groups respectively, with a mean treatment duration of 5.9 ± 1.9 days. The authors provide detailed statistical analysis using both the MANN-Whitney test and chi-square test and present highly significant improvements in both the edaravone and control groups. Further statistical analysis shows that there is no significant difference between mean NIHSS scores at either admission or discharge. However, statistical analysis shows that there was a larger reduction in palsy score in the edaravone-treated group compared to the control group ($p=0.006$).

Shinohara[72] also studied the effects of edaravone in a mixed population of stroke patients including thrombotic and lacunar stroke. The study was part of a multicenter randomized parallel-group open-label design comparing edaravone to ozagrel (Table 1). The main conclusion is that edaravone was at least as effective as ozagrel. The data shows that there is a trend for decreased NIHSS scores in edaravone-treated patients.

In the 2009 *Sinha* trial, the first published experience with edaravone outside of Japan[73], twenty two AIS patients were given 30 mg of edaravone twice daily for 14 days by infusion (Table 1). The mean time to treatment following onset was 26.5 ± 21.27 hours. The study used mRS and Barthel Index (BI) assessed up to 90 days following treatment. In the study, 68% of patients had a favorable outcome where the mean mRS score decreased from 4.01 ± 0.92 at baseline to 1.86 ± 1.07 at day 90 ($p<0.005$) and the mean BI increased from 40.00 ± 30.11 at baseline to 75.62 ± 22.86 at day 90 ($p<0.005$). This was the first confirmation that edaravone had efficacy in patients and that the effect could be observed with a long therapeutic window.

The *Toyoda* study[74] enrolling internal carotid artery (ICA) occlusion patients is an extreme test for the efficacy of edaravone because of the fatal nature of ICA occlusions in the majority of patients[75]. In the study, stroke patients with baseline NIHSS scores ≥ 15 (Mean $\pm$ SEM was 21 ± 4) were treated for 14 days with edaravone and they were compared to a historical

control (Table 2). The most obvious effect of edaravone was decreased mortality during the acute stage following ICA occlusion, where only 20% of edaravone-treated patients compared to 45% of control patients died from the stroke ($P<0.03$). Moreover, there was temporary functional outcome improvement ($p<0.03$) in edaravone-treated patients, which was not significant in all ICA occlusion survivors, but 8% of edaravone-treated patients were considered independent within 8 weeks of onset. These results are significant considering the devastating nature of this particular type of stroke.

Last, the *Unno* trial[76], which is a dose-finding trial, attempted to correlate number of ampoules of edaravone administered to patients with thrombotic, embolic and lacunar strokes with improved functional outcome. The study used a sophisticated treatment regimen design where the uncontrolled study stratified the population of enrolled patients into Tertiles with the mean number of ampoules administered as follows: Tertile 1: 4 ± 5 (Mean dose, 120mg, $n=29$), Tertile 2: 19 ± 3 (Mean dose, 570mg, $n=23$), Tertile 3: 26 ± 2 (Mean dose, 780mg, $n=20$). This should be compared to the previous design used by Otomo[65], where a cumulative dose of 840mg was used (i.e.: 30 mg b.i.d., 14 days = 840 mg). Using regression correlative analysis, the author's document a significant correlation between number of edaravone ampoules or cumulative dose used, and Functional Independence Measure Motor (FIMM) and Barthel Index (BI) outcome. Significance levels, $p=0.003$ for FIMM and $p=0.0005$ for BI were noted for cardioembolic patients, but this was not carried over to other stroke subtypes ($p>0.05$). It is interesting to note that even in the 3rd Tertile, the mean cumulative is less than that used in previous studies. This should be considered a study design shortcoming because it does not allow for direct comparison to previous studies using a standard dosing regimen.

4.1 Clinical Research Pharmacokinetics

Shibata and colleagues originally published the Phase I safety and pharmacokinetic profile of edaravone[77]. In normal volunteers, edaravone is well tolerated following single or multiple dose I.V. administration, which may be due to a short half life in the range of 0.15–5.16 hours depending on the administration regimen. The Phase I study did not evaluate edaravone using the most common treatment regimen for stroke patients (i.e.: 30mg b.i.d., 14 days). Edaravone is excreted as unmetabolized drug (~1%) or metabolized by sulfation (5–13%) or glucuronidation (68–83%) and excreted in urine within 24hours of administration. In normal volunteers, there were no adverse events (AEs).

4.2 Preclinical & Clinical Toxicology

Preclinical CeeTox™ analysis of Edaravone using an extensive panel of toxicity markers shows that the drug has no acute toxicities when a rat H4IIE hepatoma cell system was used for analysis[78]. In the assay, the estimated C_{Tox} value or sustained concentration expected to produce toxicity in a rat 14 day repeat dose study is $>300\text{ }\mu\text{M}$. However, the study noted that Edaravone was metabolically unstable and quickly metabolized by pooled microsomes from non-induced male Sprague-Dawley rats with only 28% of parent remaining after a 30 minute incubation period, which is indicative of rapid phase I metabolism via cytochrome P450 enzymes[78].

However, clinically a number of incidences of AEs have been observed in stroke trials [79]. Of the 8 stroke clinical trials with edaravone, only the Otomo study[65] and Shinohara study [72] reported AEs and SAEs in their published reports. In the Otomo study[65], the AEs were abnormal liver function, itching and nausea and SAEs were death due to exacerbation of brain infarction, sudden cardiac arrest, pneumonia and depression-induced suicide. Interestingly, in the Shinohara study[72], edaravone-induced renal AEs occurred in 5.7% of patients, hepatic AEs in 21.6% of patients and cerebrovascular disorders in 13.4% of patients. Noteworthy are death in 5 patients due to pneumonia, lymphoma and depression-related suicide. The major

edaravone AE is reported to be an increased risk of renal toxicity associated [80,81], which is reversible in 45% of patients after edaravone treatment is stopped [80]. However, 11 adverse side effects are now listed on the drug information sheet for the drug, including fulminant hepatitis[82], thrombocytopenia, rhabdomyolysis and acute lung injury. There is also a report of an increased frequency of hemorrhagic transformation when edaravone was administered to patients with cardiogenic embolism [83].

5. Edaravone in combination with thrombolytics

A few of the published clinical studies document the use of edaravone in combination with thrombolytics such as tPA and urokinase. The following studies note tPA (IV) and urokinase (UK, intra-arterial) use in patients receiving edaravone: Inatomi [68], Toyoda [74] and Unno [76]. Inatomi indicated that one patient was partially recanalized with UK. The remaining studies did not specifically comment on the adverse effects or efficacy of combination therapy. The following studies noted tPA and UK as an exclusion criteria: Ohta [71], Otomo [65] and Mishina [69].

The most intriguing finding regarding combination therapy of Edaravone and tPA was documented by Yoshifumi[84]. The authors reported preliminary findings of a clinical trial showing that patients treated with edaravone prior to administration of intravenous tPA had a reduced ICH compared to tPA-treated patients. If this edaravone effect can be reproduced, then combination therapy using a multi-arm clinical design should be considered for in the next clinical trial.

6. Prospects for the Use of Edaravone to Treat Stroke & Conclusion

Based upon 1 randomized, placebo-controlled, double-blind multicenter trial and numerous retrospective trials with a total of 669 patients with embolic, thrombotic and lacunar strokes treated with edaravone, the cumulative data suggests that some patients may benefit from the administration of edaravone. Who should receive edaravone and when?

As can be gleaned from Tables 1 and 2, edaravone has not been systematically tested for efficacy using a standard treatment regimen, except for a dose of 30mg i.v. b.i.d, but even that dose, which has not been used for a consistent duration of treatment, may not be optimal. Figure 2 presents the time to treatment for all currently available edaravone trials. In every trial to date, independent of the time to treatment, the data has been presented to show a significant and positive effect of edaravone on a clinical, functional or survival parameter measured in the study. Based upon the clinical trial data, Edaravone is most effective when administered within 24 hours following a stroke.

MCI-186 is currently being studied for safety and pharmacokinetic profile in patients with AIS in a Phase IIa multi-centre, randomized, double-blind, placebo-controlled, clinical study [85]. It is interesting to note that the trial is a 2-cohort study with 1000mg and 2000mg doses for the study and that patients will be enrolled within 24 hours of a stroke. This suggests that the standard 30mg b.i.d dosing used in all previous studies, including the Unno study[76] may not have been optimal. The original dose used in the Otomo study[65] was cited to be based upon early phase 2 dose-finding and efficacy studies[66,67], which used doses from 10–60 mg b.i.d. The higher end of the studies[66,67] is consistent with the proposed 2nd tier cohort to use 2000mg dose in patients.

There appears to be some consensus in the edaravone clinical trial literature[76] that an extended edaravone treatment period is required for maximum efficacy and this may be based upon the original Otomo study[65]. Certainly with treatment durations of 6–14 days for the clinical efficacy studies assessed in this article, it is difficult to conclude that a particular

treatment duration is most beneficial. As reported by Unno[76], the specific treatment regimen prescribed by Mitsubishi Pharmaceutical is unclear and may depend upon the severity of stroke upon admission. That should not be a factor in the further development of this therapeutic agent if a blinded randomized clinical trial is to be carried out. According to the Kageyama [86] post-marketing survey, clinically there is widespread variation in the duration of treatment and this can be seen in the studies cited in Table 2.

It is surprising that the phase IIa edaravone trial design[85] has specifically excluded thrombolytic such as tPA, UK, streptokinase, reteplase and tenecteplase. The current state-of-the-art clinical trial design, which was first attempted for NXY-059[87], but failed due to inferior pharmacological properties of the drug[13,88], used a 4-arm design to include placebo, tPA, study drug and the combination of study drug plus tPA [87]. It is conceivable that a tPA-treated population of patients that would have partial or full recanalization [10,11] plus the benefit of a multi-target drug to attenuate the deleterious effects of ischemic cascade activation [26,59] and possibly also reduce tPA-induced edema[40,84], if it were to occur, would have a better outcome(see [59]).

7. Expert Opinion

Based upon the efficacy profile of Edaravone in patients with multiple stroke subtypes and stroke severity, the drug should be further pursued to determine its utility as a neuroprotective treatment. To do that, Edaravone should be further studied in a well controlled clinical trial with standardization of dose, treatment duration and time to treatment in order to unequivocally ascertain the efficacy of Edaravone. In fact, if Mitsubishi Pharmaceuticals aims to develop Edaravone worldwide, then a recommended time to treatment window in a double blind randomized clinical trial would be in the range of 7–10 hours based upon trends of efficacy in patients with various types of stroke in the Otomo study[65] and a preclinical embolic stroke translational study[13,59]. The goal of the initial trial should be to provide evidence of significant efficacy using an optimal drug dose within a reasonable therapeutic window and not obscure efficacy by using an overly broad therapeutic window. Based upon the current literature, it does not appear that the optimal drug dose for durable neuroprotection has been established. However, with respect to patient safety, the 30 mg i.v., b.i.d. 14 days regimen used by Otomo[65] may be near the upper end of the safety limit, because renal dysfunction, which is estimated to occur in 0.04% of the treated population[80], is associated with Edaravone use at this dose.

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Figure 1. Edaravone Efficacy in AIS Patients treated within 24 hours: Data extracted from the 1993–1996 Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. There was a significant shift toward lower mRS scores of 0–1 for patients treated within 24 hours. Data from[65].

Figure 2.

Edaravone **Time to Treatment** indicated by **Study Author**. In all studies, there was a significant positive effect of Edaravone on a clinical outcome independent of the **Time to Treatment**. When only a single bar is provided, the study did not have a placebo control. References for author are as follow: Otomo[65], Inatomi[68], Mishina[69], Ohta[71], Shinohara[72], Sinha[73], Toyoda[74], Unno[76].

Table 1

Edaravone- Efficacy in AIS Patients- Randomized, Placebo-Controlled Study

Otomo[65] December 1993 - March 1996	Control (C) (125) Edaravone (E) (125) Study Type: Randomized Placebo-Controlled Double-Blind, Multicenter Stroke Type: Thrombotic & Embolic Dose- 30mg i.v., b.i.d. Treatment duration:14 days Data Analysis: mRS TT: (C) 35.2 ± 26.6 hours (E) 37.3 ± 22.6 hours	Neurological Deficit Baseline Median (C) 6 (4,11) (E) 6, (4,10) Result: Significant clinical improvement using mRS Assessment mRS (0–2) 3 month score (C) 66% (E) 73% (p=0.048) 6 month score (C) 67% (E) 73% (p=0.0112) 12 month score (C) 66% (E) 72% (p= 0.0248)
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Table 2

Edaravone- Efficacy in AIS Patients- Retrospective Analyses

Study[REF] (Alphabetical)	Trial Information	Clinical Endpoints																		
Inatomi [68] October 2000 - September 2002	Control (C) (101) Edaravone (E) (141)	NIHSS SCORES <table><tr><th></th><th>0-7</th><th>8-15</th><th>16-20</th><th>21-40</th><th>mean</th></tr><tr><td>(C)</td><td>4/6 (27)</td><td>12/8 (27)</td><td>18/14 (24)</td><td>30/31(23)</td><td>15/14</td></tr><tr><td>(E)</td><td>4/2 (31)*</td><td>12/9 (34)</td><td>18/16 (39)</td><td>26/26(37)</td><td>16/14</td></tr></table> Result: Data given as NIHSS on admittance (Day 0 /Day 10). *Significantly different from control for NIHSS 0-7 (p=0.013). A 2 point NIHSS improvement was noted with edaravone treatment.		0-7	8-15	16-20	21-40	mean	(C)	4/6 (27)	12/8 (27)	18/14 (24)	30/31(23)	15/14	(E)	4/2 (31)*	12/9 (34)	18/16 (39)	26/26(37)	16/14
			0-7	8-15	16-20	21-40	mean													
	(C)		4/6 (27)	12/8 (27)	18/14 (24)	30/31(23)	15/14													
	(E)		4/2 (31)*	12/9 (34)	18/16 (39)	26/26(37)	16/14													
	Study Type: Retrospective																			
	Historical Controlled																			
Stroke Type: Cardioembolic																				
Dose- 30mg i.v., b.i.d.																				
Mishina[69] June 1999 - May 2002	Treatment duration: 7 days	NIHSS BASELINE SCORE (C) 5.1 ± 4.5 (E) 3.3 ± 2.8 Result: With edaravone treatment, there was an odds ratio of 6.49 (95% confidence interval, 1.35 to 50.32; p=0.04) for good outcome, i.e. mRS ≤ 2 for patients with NIHSS ≤ 8.																		
	Data Analysis: NIHSS (Day 0)/NIHSS (Day 10)																			
	TT: Undefined, but ≤24hours																			
	Control (C) (49) Edaravone (E) (21)																			
	Study Type: Retrospective																			
	Stroke Type: Lacunar																			
Ohta[71] January 2004 - June 2007	Dose- 30mg i.v., b.i.d.	NIHSS BASELINE SCORE (C) 2.0 ± 1.3 Admit to 1.0 ± 1.2 Discharge (E) 2.2 ± 1.0 Admit to 0.7 ± 10.7 Discharge Result: Mean NIHSS reduction in the edaravone-treated group was significantly different (p=0.007) from control (1.5 ± 1.0 vs. 1.0 ± 1.1). There was also a modest, but significant (p=0.006) reduction of NIHSS palsy scores in the edaravone-treated group (1.0 ± 1.0																		
	Treatment duration: 14 days																			
	Data Analysis: NIHSS and mRS 30 day																			
	TT: ≤24hours																			
	Control (C) (65) Edaravone (E) (59)																			
	Study Type: Retrospective																			
Ohta[71] January 2004 - June 2007	Stroke Type: Lacunar	NIHSS BASELINE SCORE (C) 2.0 ± 1.3 Admit to 1.0 ± 1.2 Discharge (E) 2.2 ± 1.0 Admit to 0.7 ± 10.7 Discharge Result: Mean NIHSS reduction in the edaravone-treated group was significantly different (p=0.007) from control (1.5 ± 1.0 vs. 1.0 ± 1.1). There was also a modest, but significant (p=0.006) reduction of NIHSS palsy scores in the edaravone-treated group (1.0 ± 1.0																		
	Dose- 30mg i.v., b.i.d.																			
	Treatment duration: 2-10																			
	Control (C) (49) Edaravone (E) (21)																			
	Study Type: Retrospective																			
	Stroke Type: Lacunar																			

Study[REF] (Alphabetical)	Trial Information	Clinical Endpoints
	days; mean duration 5.9 ± 1.9 days. Data Analysis: NIHSS entry and discharge TT: (C) 9.8 ± 7.0 hours (E) 9.2 ± 5.8 hours	vs. 0.5 ± 1.1). Moreover, a larger population (91.5%) of edaravone-treated patients at discharge had a favorable outcome compared to control (78.5%) ($p=0.044$ chi-square).
Shinohara[72] August 2004 - October 2006	Edaravone (199) Study Type: Open-label unblinded, uncontrolled Stroke Type: Thrombotic and Lacunar Dose- 30mg i.v., b.i.d. Treatment duration: 14 days Data Analysis: NIHSS entry and discharge TT: (E) 13.2 ± 6.0 hours	NIHSS BASELINE SCORE (E) 3.7 ± 2.3 Admittance 14 day score 0–1 98/190 patients (51.6%) 1 month score 0–1 117/191 patients (61.6%) 3 month score 0–1 135/190 patients (70.7%) Result: Trend for improvement from mean baseline to 0–1 score.
Sinha[73] January 2008 - July 2008	Edaravone (22) Study Type: Unblinded Uncontrolled Trial. Stroke Type: Not given Dose- 30mg i.v., b.i.d. Treatment duration: 14 days Data Analysis: mRS and BI TT: 26.5 ± 21.27 hours	(a) NIHSS BASELINE SCORE 10.62 ± 8.86 7 day 6.62 ± 7.48 ($p<0.05$) 14 day 5.12 ± 6.03 ($p<0.05$) 30 day 4.12 ± 4.64 ($p<0.05$) 90 day 3.12 ± 4.71 ($p<0.005$) (b) mRS BASELINE 4.01 ± 0.92 7 day 3.62 ± 1.18 ($p<0.05$) 14 day 2.87 ± 1.55 ($p<0.05$) 30 day 2.25 ± 1.28 ($p<0.005$) 90 day 1.86 ± 1.07 ($p<0.005$) Result: Significant decrease in both NIHSS and mRS compared to baseline up to 90 days following the stroke.
Toyodal[74] October 1999 -	Control (C) (31)	NIHSS BASELINE SCORE

Study[REF] (Alphabetical)	Trial Information	Clinical Endpoints
July 2002	Edaravone (E) (30) Study Type: Retrospective Historical Control Stroke Type: Internal carotid artery occlusion Dose- 30mg i.v., b.i.d. Treatment duration: 14 days Data Analysis: NIHSS and mRS TT: Undefined, but ≤6hours	(C) 21 ± 3 (E) 21 ± 4 Result: Frequency of independence (i.e. mRS grade of 1 or 2) increased in edaravone-treated patients compared to control (p<0.1). Temporary functional outcome improvement (p<0.03) in edaravone-treated patients. Improved acute survival rate.
Unno[76] July 2006 - November 2007	Edaravone (E) (72) Study Type: Retrospective, Historical Control Stroke Type: cardioembolic thrombotic, lacunar Dose- 30mg i.v., b.i.d. Treatment duration: 14 days Data Analysis: Functional Independence Measure Motor (FIMM) and Barthel Index (BI) TT: Undefined, but ≤24hours	Dosing Regimen: Tertile 0–14 ampoules (n=21) 15–23 ampoules (n=27) 24–33 ampoules (n=24) Result: Regression analysis performed indicated a significant correlation between number of edaravone ampoules used and FIMM and BI outcome. p=0.003 for FIMM and p=0.0005 for BI in cardioembolic patients. There was no significant correlation for other stroke subtypes.

NIHSS- National Institutes of Health Stroke Scale, mRS- Modified Rankin Scale, BI- Barthel Index, b.i.d- twice a day, TT- time to treatment.

Drug Summary Box

Drug name	Edaravone
Phase	Launched
Launched indication	Cerebral infarction
Pharmacology description	Free radical scavenger
Route of administration	Parenteral, intravenous
Chemical structure
Pivotal trial(s)	Edaravone Acute Ischemic Stroke Group

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