Beyond free radical scavenging: Beneficial effects of edaravone (Radicut) in various diseases (Review)

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Abstract. Free radicals play an important role in the pathogenesis of a variety of diseases; thus, they are an attractive target for therapeutic intervention in these diseases. Compounds capable of scavenging free radicals have been developed for this purpose and some, developed for the treatment of cerebral ischemic stroke, have progressed to clinical trials. One such scavenger, edaravone, is used to treat patients within 24 h of stroke. Edaravone, which can diffuse into many disease-affected organs, also shows protective effects in the heart, lung, intestine, liver, pancreas, kidney, bladder and testis. As well as scavenging free radicals, edaravone has anti-apoptotic, anti-necrotic and anti-cytokine effects in various diseases. Here, we critically review the literature on its clinical efficacy and examine whether edaravone should be considered a candidate for worldwide development, focusing on its effects on diseases other than cerebral infarction. Edaravone has been safely used as a free radical scavenger for more than 10 years; we propose that edaravone may offer a novel treatment option for several diseases.

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Contents

1. Introduction

Many compounds have been evaluated as free radical scavengers for the treatment of cerebral ischemic stroke, but few have been successful in studies conducted in Western countries. By contrast, trials conducted by Japanese researchers have been more successful (1). Several free radical scavengers have been developed and several of these (e.g., ebselen, tirilazad and NXY-059) have progressed to clinical trials (2). Ebselen and tirilazad produced inadequate therapeutic effects in patients with cerebral infarction and further studies were terminated (3,4), while the Stroke-Acute Ischemic NXY Treatment II trial showed that NXY-059 was not effective against cerebral infarction when administered within 4 h of onset of symptoms (5).

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, MCI-186, Radicut; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was the first neuroprotective drug to be introduced worldwide. Since 2001, it has been used in Japan to treat many patients with cerebral ischemic stroke (6-8). It is

currently approved only in Japan. The free radical scavenger edaravone exerts anti-oxidant effects by inhibiting hydroxyl radical-dependent and independent lipid peroxidation (7,9). This anti-oxidant activity, which is proposed to be the main mechanism of action of edaravone, may protect against free radical-related injuries following cerebral ischemic stroke (10). Edaravone was also shown to suppress increases in hydroxyl and superoxide anion radical levels in several models of cerebral ischemic stroke (11,12).

Edaravone exerts effects that are unrelated to its free radical scavenging actions and that may be useful in the treatment of diseases other than cerebral infarction. To the best of our knowledge, potential use of edaravone in the treatment of other diseases has not been reviewed elsewhere. Therefore, in the present review, we discuss the most recent research on the use of edaravone, primarily in animal models of various diseases. We also assess its potential use in the treatment of these diseases.

2. Pharmacological effects of edaravone in non-neurologic diseases

Effects of edaravone on apoptosis. Anti-apoptotic effects of edaravone have been reported in studies of several diseases, including non-neurologic diseases. In a rat coronary occlusion model, edaravone reduced the myocardial infarction area, maintained myocardial ATP content, decreased mitochondrial swelling, reduced cytochrome c release, increased the expression of BCl-2 and reduced the number of apoptotic cells and DNA fragmentation (13). Edaravone ameliorated the progression of experimental autoimmune myocarditis (EAM), it improved left ventricular (LV) function and decreased the number of TUNEL-positive cells in the LV of rats with EAM (14). Edaravone attenuated apoptotic cell death in rabbits with bleomycin-induced pulmonary injury (15).

Edaravone blunted ischemia/reperfusion (I/R)-induced hepatic dysfunction and hepatic apoptosis in rats (16). Edaravone treatment blunted the carbon tetrachloride (CCL_4)-induced elevation in serum alanine aminotransferase (ALT), serum lactate dehydrogenase (LDH), serum total bilirubin, hepatic fatty degeneration, hepatic steatosis and hepatic apoptosis in rats (17,18). *In vitro*, edaravone appears to protect hepatocytes from Fas-induced mitochondrial-dependent apoptosis by regulating mitochondrial Bcl-xL and Bax in mice with fulminant hepatic failure (19).

In streptozotocin-induced diabetic rats, edaravone promoted engraftment of intraportally transplanted islet cells, ameliorated hyperglycemia, increased insulin secretion and the number and size of islet β cells morphologically and decreased the number of TUNEL-positive cells in each islet (20).

Edaravone attenuated cisplatin-induced renal dysfunction, renal tubular damage, mitochondrial damage, real protein oxidation and tubular apoptosis in rats (21).

Edaravone also suppressed X-ray-induced apoptosis in the human T-cell leukemia cell line, MOLT-4 (22,23).

Effects of edaravone on necrosis. Anti-necrotic effects of edaravone have been reported in studies of multiple diseases, including non-neurologic diseases. For example, edaravone reduced the area of necrotic myocardium in rats (24) and rabbits (25) in myocardial I/R models. Edaravone blunted the I/R-induced elevation in hepatic dysfunction and hepatic necrosis in rats (16,26). Edaravone treatment also blunted CCL_4-induced hepatic necrosis in rats (17). Edaravone treatment blunted the I/R-induced elevation in serum ALT, hepatic congestion, hepatic vacuolization and hepatic necrosis in rats (27).

In a rat sodium taurocholate-induced pancreatitis model, edaravone reduced plasma amylase levels, pancreatic myeloperoxidase (MPO; an indicator of neutrophil infiltration) activity, necrosis, edema and inflammatory cell infiltration (28).

Edaravone reversed cisplatin-induced renal dysfunction in rats, including an elevation in blood urea nitrogen and creatinine and histological changes, such as vacuolization, necrosis and protein casts (29). Edaravone attenuated renal dysfunction and acute tubular necrosis in a rat I/R acute renal failure (ARF) model (30).

Edaravone also reduced cell swelling, tubular vacuolization and necrosis in rat testis with I/R injury (31).

Effects of edaravone on oxidative stress. Anti-oxidant effects of edaravone have been reported in studies of multiple diseases, including non-neurologic diseases. Edaravone decreased serum concentrations of creatine kinase-MB isoenzymes, attenuated infarct size and improved ventricular ejection in 80 patients with acute myocardial infarction (AMI) (32). Edaravone attenuated infarct size, reperfusion arrhythmia and serum thioredoxin (a marker of oxidative stress) in 101 patients with AMI (33). Edaravone preserved coronary microvascular endothelial function, increased nitric oxide (NO) and decreased ROS in dogs with I/R injury (34). Edaravone significantly reduced MI size and improved cardiac function and LV remodeling by decreasing hydroxyl radicals and superoxide in the myocardium and increasing the production of NO during reperfusion in rabbits (35). Furthermore, in rats, edaravone prevented lethal reperfusion ventricular tachyarrhythmias and deteriorated cardiac function with ischemia and I/R injuries through inhibition of lipid peroxidation by scavenging free radicals (36). The addition of edaravone to cardioplegic solution ameliorated myocardial functional impairment by reducing oxidative stress after cardioplegic arrest in rats as well (37). Edaravone reduced myocardial oxidative stress overload with DNA damage, decreased myocardial protein carbonyl contents, the myocardial thiobarbituric acid reactive substance products, the formation of hydroxyl radicals and cytotoxic activities of lymphocytes in rats with EAM. It protected against acute EAM in rats by scavenging hydroxyl free radicals, resulting in the suppression of autoimmune-mediated myocardial damage associated with a reduced oxidative stress state (38). Edaravone ameliorated the progression of EAM in rats, improved LV function and decreased LV expression of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) sub-unit [p67 (phox)] (14). Edaravone also exerted a cardioprotective action by inhibiting lipid peroxidation in a pig heart transplantation model (39). In an *in vitro* study, edaravone reduced I/R-induced cell death by attenuating ROS production in rabbit cardiomyocytes (40).

Edaravone blunted I/R-induced pulmonary dysfunction, pulmonary focal hyaline membrane formation, pulmonary neutrophil infiltration, pulmonary interstitial edema and oxidative stress markers, such as malondialdehyde (MDA), in

dogs (41). Edaravone improved the survival rate of I/R-induced rabbits, reduced the production of hydroxyl radicals and MDA, increased the activities of glutathione peroxidase and superoxide dismutase (SOD) and reduced mitochondrial damage in lung tissue (42). In an isolated rat lung model, edaravone blunted the I/R-induced elevation in pulmonary dysfunction by suppressing pulmonary MDA and MPO activity, phospholipase (PL) A_2 activation, which otherwise partially mediated edema formation, and neutrophil extravasation mediated by platelet-activating factor (PAF) receptor (43). In mice with bleomycin-induced pulmonary injury, edaravone improved the survival rate, reduced fibrotic change and the production of lipid hydroperoxide (LPO) in bronchoalveolar lavage fluid (BALF) and serum and increased the production of prostaglandin E_2 in BALF (44).

Edaravone reduced I/R-induced small intestine injury, the levels of intraluminal protein and hemoglobin (an index of mucosal injury), thiobarbituric acid-reactive substances (TBARS; indicators of lipid peroxidation), tissue-associated MPO activity and multiple erosions and bleeding in rats (45). In a rat model of the acute phase of Crohn's disease, edaravone reduced the ulcer index, histological damage score, markers of oxidative damage, such as MPO activity and TBARS concentration, and ameliorated mesenteric indomethacin-induced longitudinal ulceration of the small intestine (46).

Edaravone improved the survival rate of LPS-treated rats and inhibited the increase in serum ALT levels and 4-hydroxynonenal (HNE)-modified proteins in rat liver tissue (47). Edaravone markedly improved the survival rate of I/R-induced liver injury in rats and decreased the levels of serum aspartate transaminase (AST), serum ALT and MPO activity (48). Similarly, edaravone treatment blunted I/R-induced elevation in serum ALT, serum hyaluronic acid (HA), lipid peroxidation and free radicals in rat liver (49). Edaravone ameliorated I/R-induced hepatic dysfunction and lipid peroxidation of perfusate in rats (50). Edaravone protects against mitochondrial injury, which prevents mitochondrial lipid peroxidation, inhibits the decrease in glutathione activity and improves I/R-induced hepatic energy metabolism in rats (51). Edaravone blunted I/R-induced hepatic dysfunction and an increase in MDA levels in rats (16). Furthermore, in rats, edaravone reduced hepatic I/R injury by minimizing hepatic lipid peroxidation (52). Edaravone treatment blunted CCL_4-induced increases in the levels of oxidative stress markers, such as MDA, 4-HNE and 8-hydroxydeoxyguanosine (OHdG), in rats with hepatic injury (17,26). Edaravone treatment was also shown to blunt I/R-induced elevation in hepatic lipid peroxidation in rats (27). In another study, edaravone prevented LPS-induced liver injury after partial hepatectomy by attenuating oxidative damage and by reducing the production of MDA, NO and iNOS in rats (53). In this study, edaravone markedly improved the survival rate of LPS-treated rats after hepatectomy and inhibited increases in serum AST and LDH (53). Histopathological analysis revealed that edaravone also prevented inflammatory changes in the liver, kidney and spleen (53). An *in vitro* study involving primary cultures of rat hepatocytes further revealed that edaravone directly inhibits the induction of iNOS gene expression at the steps of its promoter transactivation and mRNA stabilization in IL-1β-stimulated hepatocytes (54).

In a rat closed duodenal loop (CDL)-induced pancreatitis model, edaravone treatment tended to reduce ascites volume and to inhibit increases in wet pancreatic weight (55). Edaravone also tended to reduce microscopic mucosal damage scores and pancreatic tissue lipid peroxide levels (55).

Edaravone protected renal tubular epithelial cells and vascular endothelial cells, ameliorated renal dysfunction and inhibited increases in the levels of MDA and 8-OHdG in a canine I/R injury model (56). In a rat I/R ARF model, edaravone attenuated renal dysfunction, ROS production and lipid peroxidation (30). Edaravone was able to delay and improve urinary protein excretion in accordance with urinary 8-OHdG excretion in puromycin nephrosis in rats (57). Edaravone reduced urinary protein and the levels of glomerular TBARS in rats with puromycin nephrosis (58). An *in vitro* study revealed that edaravone attenuated cisplatin-induced cell death, mitochondrial transmembrane potential loss and ROS production in murine proximal tubular cells (21).

Edaravone protected the contractile response during both field stimulation and carbachol exposure and reduced MDA levels after I/R-induced damage in the rat bladder (59). Acute urinary retention (AUR) and subsequent catheterization caused lipid peroxidation and oxidative DNA damage in the rat bladder (60). Edaravone induced a decrease in blood flow in the bladder during urinary retention and subsequent catheterization (60). Edaravone protected the contractile responses to both carbachol and KCl and reduced the levels of MDA and 8-OHdG after AUR and subsequent catheterization-induced bladder dysfunction in rats (60).

Similarly, in an I/R-induced rat testicular torsion model, edaravone reduced NO_2-NO_3 (a marker of NO production), MDA, 8-OHdG and MPO (31).

Edaravone suppressed free radicals (e.g. NO and total hydroperoxide), thereby maintaining mean arterial pressure (MAP) and prolonging survival time in a neonatal sepsis cecal ligation and perforation (CLP) model in piglets (61).

Edaravone treatment significantly reduced the levels of free radical precursors, such as MDA and xanthine oxidase, and their metabolites in the serum and tissue compared to controls in burn rats (62).

Edaravone diminished intestinal neutrophil lipid peroxidation and bacterial translocation in a rat hemorrhagic shock (HS) model (63). Furthermore, edaravone improved the survival rate in a rat HS model without resuscitation (64).

The administration of high doses of methamphetamine causes the degeneration of striatal dopaminergic fibers in the brains of rodents, and oxidative stress appears to be one of the main neurotoxic factors (65). Edaravone protected against methamphetamine-induced neurotoxicity in the striatum by blocking peroxynitrite production in mice (65). Edaravone blocked the increase in 3-nitrotyrosine (a biomarker of ROS) immunoreactivity and the activation of astrocytes (65).

Effects of edaravone on cytokines. Anti-cytokine effects of edaravone have been reported in studies of various non-neurologic diseases. Edaravone suppressed plasma monocyte chemoattractant protein-1 (MCP-1), improved left ventricular ejection fraction and reduced rehospitalization due to heart failure in 45 patients with AMI (66). Edaravone reduced myocardial IL-1β-positive cells in rats with EAM (38).

Edaravone protected cardiac function and reduced infarct size via a decrease in myocardial TNF-α production induced by I/R injury in rats (67). Edaravone reduced the number of IL-1β-positive cells in rats with acute EAM as well (68).

In the LPS-induced acute lung injury mouse model, edaravone prevented lung injury and attenuated inflammatory cells and pro-inflammatory cytokine production, such as IL-6, TNF-α, keratinocyte-derived chemokine and macrophage inflammatory protein (MIP)-2 in BALF (69). Edaravone attenuated inflammatory cells, interstitial fibrosis, peribronchial fibrosis and transforming growth factor-β-positive cells in rabbits with bleomycin-induced pulmonary injury (15).

In the rat small intestine, edaravone reduced I/R injury and the levels of cytokine-induced neutrophil chemoattractant (CINC)-1 (a member of the IL-8 family) protein and mRNA (45).

Edaravone prevented LPS-induced liver injury by both inhibition of inflammatory cell recruitment and expression of inflammatory cytokines in the rat liver (47). Moreover, mRNA expression levels of MIP-2, MCP-1 and MCP-5 were attenuated by edaravone (47). As a result, increases in the number of infiltrating inflammatory cells and mRNA expression of inflammatory cytokines, such as TNF-α and IL-6, were significantly blunted by edaravone in the rat liver (47). This reduction was accompanied by a significant reduction in their serum levels (47). Edaravone markedly improved the survival rate of I/R-induced liver injury and decreased the levels of serum AST, serum ALT and IL-6 mRNA in rats (48). Edaravone treatment blunted I/R-induced elevation in serum ALT (49), serum HA (49), hepatic TNF-α mRNA (49), serum TNF-α (49), perfusate TNF-α (50), perfusate IL-1β (50), serum IL-6 (49), Kupffer cell TNF-α mRNA (49) and leukocyte infiltration (49) in the rat liver. Edaravone treatment blunted CCL_4-induced elevation in serum IL-6, serum IL-10, serum TNF-α, hepatic TNF-α mRNA, hepatic IL-4 mRNA, hepatic IL-6 mRNA and hepatic IL-10 mRNA in rats with hepatic injury (17). Edaravone blunted I/R-induced elevation in IL-10 of perfusate in rats (26). Edaravone treatment blunted I/R-induced elevation in hepatic tissue monocytes and neutrophils, hepatic IL-1β, CINC-2, MIP-2, MCP-1, MIP-1α, MIP-1α and intercellular adhesion molecule (ICAM)-1 mRNA in rats (27). In another study, edaravone prevented LPS-induced liver injury after partial hepatectomy by reducing the production of CINC and inflammatory cytokines (e.g., TNF-α, IL-2, IL-1β and interferon-γ); these changes were at least partly mediated by inhibition of NF-κB activation in rats (53).

In a piglet CLP model, edaravone delayed the TNF-α surge and prevented HMGB1 elevation, thereby maintaining MAP and prolonging survival time (61).

Effects of edaravone on ER stress. Edaravone has been shown to reduce ER stress in a study of myocarditis. Edaravone ameliorated the progression of EAM, improved LV function and decreased the ER stress signaling proteins GRP78 and caspase-12 in rats (14).

Effects of edaravone on heat shock proteins (HSPs). Anti-HSP effects of edaravone have been reported in several disease models. Edaravone reduced the levels of HSP 70 (a marker of stress) and its mRNA in an I/R-induced rat testicular torsion model (31). Edaravone also markedly reduced the expression levels of HSP 70 and its mRNA and prevented bladder dysfunction caused by AUR and subsequent catheterization in rats (60).

Effects of edaravone on tumor markers. Edaravone has been reported to reduce markers of tumorigenesis. Edaravone suppressed X-ray-induced apoptosis by inhibiting p53 in MOLT-4 cells (22).

Effects of edaravone on cell adhesion molecules. Edaravone reduced the release of adhesion molecules, such as P-selectin, from vascular endothelial cells in rats with AMI (67). Furthermore, edaravone reduced hepatic I/R injury and hepatic E-selectin mRNA in rats (52). Histologically, edaravone reduced E-selectin immunoreactivity and neutrophil accumulation in rat hepatic sections (52). In severe hindlimb ischemia, edaravone attenuated neutrophilic infiltration, the serum level of soluble ICAM-1 and muscular edema in a rat model of myonephropathic metabolic syndrome (70).

3. Conclusion

The findings of research performed to date demonstrate the potential applications of edaravone for the treatment of multiple diseases, in addition to its established use in cerebral infarction. However, edaravone is currently used only to treat cerebral infarction patients in Japan. Since oxidative stress is observed in a wide variety of diseases, the abnormal generation of free radicals may underlie the etiology and aggravation of many of these diseases. Therefore, the potential therapeutic effects of edaravone in patients with various diseases should be considered. In addition to its free radical scavenging effects, edaravone has shown anti-apoptotic, anti-necrotic and anti-cytokine effects in animal models of various diseases. It is therefore important to evaluate the clinical efficacy of edaravone treatment in the diseases described above. In fact, it was recently demonstrated that edaravone is beneficial in patients with AMI (33). Clearly, further clinical studies are required to confirm the effects of edaravone observed in animal models of diseases.

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