Beyond neurological disease: New targets for edaravone (Review)

KIYOSHI KIKUCHI[1*], HISAAKI UCHIKADO[2*], NAOHISA MIYAGI[1], YOKO MORIMOTO[3], TAKASHI ITO[4], SALUNYA TANCHAROEN[5], NAOKI MIURA[6], KEI MIYATA[4], ROKUDAI SAKAMOTO[1], CHIEMI KIKUCHI[7], NARUMI IIDA[8], NAOTO SHIOMI[9], TERUKAZU KURAMOTO[10] and KO-ICHI KAWAHARA[4]

[1]Department of Neurosurgery, Yame Public General Hospital, Yame 834-0034; [2]Department of Neurosurgery, Kurume University School of Medicine, Kurume 830-0011; [3]Department of Restorative Dentistry and Endodontology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima 890-8544; [4]Division of Laboratory and Vascular Medicine, Field of Cardiovascular and Respiratory Disorders, Department of Advanced Therapeutics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima 890-8520, Japan; [5]Department of Pharmacology, Faculty of Dentistry, Mahidol University, Rajthevee, Bangkok 10400, Thailand; [6]Veterinary Teaching Hospital and Laboratory of Diagnostic Imaging, Faculty of Agriculture, Kagoshima University, Kagoshima 890-0065; [7]Department of Rehabilitation, Nishida Koutoku Hospital, Saiki, Oita 876-0047; [8]Research Laboratory, Kohjin Co., Ltd., Saiki, Oita 876-8580; [9]Emergency Department, Saiseikai Shiga Hospital, Rittou, Shiga 520-3046; [10]Department of Neurosurgery, Omuta City General Hospital, Omuta, Fukuoka 836-8567, Japan

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Abstract. Free radicals play major roles in the pathogenesis of tissue damage in many diseases and clinical conditions, and the removal of free radicals may offer a treatment option. Several modulators of free radical scavenger pathways have been developed and some have progressed to clinical trials. One such agent, edaravone, was approved in 2001 in Japan for the treatment of cerebral infarction. It has since been shown that edaravone can diffuse into many organs and, in addition to its effects on hydroxyl radical removal, edaravone modulates inflammatory processes, matrix metalloproteinase levels, nitric oxide production, apoptotic cell death, and necrotic cell death. Edaravone also exerts protective effects in a number of animal models of disease and tissue damage, including models of myocardial, lung, intestinal, liver, pancreatic and renal injury. Together with the proven safety of edaravone following 9 years of use as a modulator of free radical scavenging pathways in neurological disease, these additional effects of edaravone suggest that it may offer a novel treatment for several non-neurological diseases and clinical conditions in humans.

Correspondence to: Dr Ko-ichi Kawahara, Division of Laboratory and Vascular Medicine, Field of Cardiovascular and Respiratory Disorders, Department of Advanced Therapeutics, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
E-mail: telo@m3.kufm.kagoshima-u.ac.jp

*Contributed equally

Abbreviations: ALI, acute lung injury; ALT, alanine amino-transferase; AST, aspartate transaminase; AMI, acute myocardial infarction; AUR, acute urinary retention; BALF, bronchoalveolar lavage fluid; CCl_4, carbon tetrachloride; CINC, cytokine-induced neutrophil chemoattractant; EAM, experimental autoimmune myocarditis; HMGB-1, high-mobility group box 1; HS, hemorrhagic shock; HSP, heat-shock protein; ICAM, intercellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; I/R, ischemia/reperfusion; LDH, lactate dehydrogenase; LPS, lipopoly-saccharide; LV, left ventricle; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MI, myocardial infarction; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; NO, nitric oxide; 8-OHdG, 8-hydroxydeoxyguanosine; PAF, platelet-activating factor; ROS, reactive oxygen species; TBA, thiobarbituric acid; TNF, tumor necrosis factor

Key words: edaravone, free radical scavenger, cerebral infarction, non-neurological disease

Contents

1. Introduction

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 and, since 2001, has been used in Japan to treat patients with cerebral infarction (1-3).

Several free radical scavengers have been developed, and some of these, including ebselen, tirilazad, and NXY-059, have progressed to clinical trials (4). However, trials of ebselen and tirilazad in patients with cerebral infarction were terminated because of inadequate therapeutic effects (5,6), and NXY-059 was shown to be ineffective against cerebral infarction when administered within 6 h of the onset of symptoms in the Stroke-Acute Ischemic NXY Treatment II trials (7).

In contrast, clinical trials have shown that administration of edaravone within 72 h of cerebral infarction significantly reduced infarct volume and provided sustained benefits over a 3-month follow-up period (8,9). More recently, Unno *et al* reported that the total dose of edaravone was associated with rehabilitation gain (10). Edaravone has also been administered within 24 h of cerebral infarction in patients with lacunae, large-artery atherosclerosis, and cardioembolic cerebral infarction (11).

Edaravone is a low-molecular-weight agent that readily crosses the blood-brain barrier, and its activity is therefore not limited to the vascular compartment (12,13). It has been shown that edaravone exerts other effects, in addition to its direct antioxidant activity, that might make edaravone useful in the treatment of many non-neurological diseases and clinical conditions. Of particular interest is the potential use of edaravone in myocardial, lung, intestinal, liver, pancreatic, and renal injury. To the best of our knowledge, there have been no reviews of the therapeutic potential of edaravone beyond neurological disease. Therefore, the aim of this review is to present the current state of research on the effects of edaravone in animal models of various non-neurological diseases and conditions, and to highlight the potential for the use of edaravone in their treatment.

2. Myocardial injury

Reperfusion after myocardial infarction (MI) greatly exacerbates ischemia-related myocardial injury (14) via excessive accumulation of free radicals, which damage the myocardium (15). Edaravone protects against myocardial injury following ischemia/reperfusion (I/R) in patients with acute MI (AMI) (12). Monocyte chemoattractant protein 1 (MCP1; also called CCL2) plays an important role in the pathogenesis of acute coronary syndrome (16), and one study demonstrated that edaravone suppressed plasma MCP1, improved the left ventricular ejection fraction, and reduced rehospitalization due to heart failure in patients with AMI (16). In other studies of patients with AMI, edaravone was reported to reduce infarct size, reperfusion arrhythmia, and levels of serum thioredoxin, a marker of oxidative stress (17), in addition to decreasing serum concentrations of creatine kinase-MB isoenzymes and improving ventricular ejection (18).

Animal experiments have revealed protective effects of edaravone against myocardial I/R injury in an AMI model and in a transplantation model (19,20). Edaravone reduced the myocardial necrotic area following myocardial I/R in rats (21) and in rabbits (22). Edaravone also prevented lethal ventricular tachyarrhythmias upon reperfusion and deteriorations in cardiac function following ischemia and I/R in rats, by inhibiting lipid peroxidation (23). In an experimental rat model of coronary occlusion, edaravone reduced the MI area, maintained adequate myocardial ATP content, decreased mitochondrial swelling, reduced cytochrome-c release, increased the expression of Bcl2, and reduced the number of apoptotic cells and DNA fragmentation (24). Edaravone also protected cardiac function in rats and reduced infarct size by decreasing the production of tumor necrosis factor α (TNF-α) in the myocardium exposed to I/R injury, and by reducing the release of adhesion molecules, such as P-selectin, from vascular endothelial cells (25). In rabbits, edaravone significantly reduced MI size and improved cardiac function and left ventricle (LV) remodeling by decreasing hydroxyl radicals and superoxide levels in the myocardium and increasing the production of nitric oxide (NO) during reperfusion (14). Edaravone was also reported to preserve coronary microvascular endothelial function, increase NO levels, and decrease reactive oxygen species (ROS) levels in dogs with I/R injury (26).

Cardioplegic arrest is the main technique used for myocardial protection during open-heart surgery; however, it can lead to myocardial injury during reperfusion (20). Free radical scavengers attenuate I/R injury in various settings (20), and the addition of edaravone to the cardioplegic solution attenuated myocardial dysfunction following cardioplegic arrest in rats by suppressing oxidative stress (20). Edaravone also exerted cardioprotective effects in a pig heart transplantation model by inhibiting lipid peroxidation (19). *In vitro*, edaravone reduced I/R-induced cell death by attenuating ROS production in rabbit cardiomyocytes (27).

Plasma ROS levels are often elevated in patients with heart failure (28). Acute myocarditis is a potentially lethal disease that frequently precedes the development of acute and chronic heart failure. Two mechanisms have been proposed to explain how myocarditis progresses into heart failure: the first involves persistent viral or etiologic agent infection, and the second involves progressive autoimmune myocardial injury. Autoimmune giant cell myocarditis in rats mimics human fulminant myocarditis with heart failure (29). In rats with acute experimental autoimmune myocarditis (EAM), edaravone reduced the number of interleukin (IL)-1β-positive cells (30). In this animal model, edaravone reduced myocardial IL-1β-positive cells and myocardial oxidative stress overload with DNA damage, and decreased myocardial protein carbonyl content, myocardial thiobarbituric acid (TBA)-reactive substances, the formation of hydroxyl radicals, and the cytotoxic activities of lymphocytes. Furthermore, edaravone protected against acute EAM by scavenging hydroxyl free radicals and reducing oxidative stress, which ultimately suppressed autoimmune-mediated myocardial damage (31). In another study, edaravone was reported to ameliorate the progression of EAM, improve LV function, decrease LV expression of the nicotinamide adenine dinucleotide phosphate oxidase subunit p67-phox and endoplasmic reticulum stress signaling proteins (GRP78, caspase 12) and to reduce the

number of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells in rats with EAM (32).

3. Lung injury

Several recent studies have evaluated the potential use of edaravone to treat lung injury induced by I/R in animal models (33-35), lipopolysaccharide (LPS) (36), and bleomycin (37,38). Lung I/R injury is a common problem encountered in many clinical conditions, including lung transplantation and cardiopulmonary bypass (33-35). In dogs, 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) (33).

In an isolated rat lung model, edaravone abrogated I/R-induced elevation in pulmonary dysfunction by suppressing increases in pulmonary MDA levels; myeloperoxidase (MPO) activity as a marker for neutrophil infiltration; phospholipase A_2 activation, which mediates edema formation; and neutrophil extravasation via the platelet-activating factor (PAF) receptor (35). In rabbits, edaravone reduced the production of hydroxyl radicals and MDA, and increased the activities of glutathione peroxidase and superoxide dismutase, which reduced damage to the mitochondria and lung tissue and thus improved the survival rate following I/R (34).

LPS-induced injury is often a factor in the etiology of various lung diseases, including acute lung injury (ALI) and adult respiratory distress syndrome (36). In the LPS-induced ALI mouse model, edaravone prevented lung injury and attenuated inflammatory cell activation and the release of pro-inflammatory cytokines, such as IL-6, TNF-α, keratinocyte-derived chemokine, and macrophage inflammatory protein (MIP)-2 by lung macrophages into bronchoalveolar lavage fluid (BALF) (36).

The bleomycin-induced pulmonary fibrosis animal model is useful to examine the mechanisms involved in pulmonary fibrosis, particularly the effects of oxygen free radicals (37,38). In rabbits with bleomycin-induced pulmonary injury, edaravone attenuated the activation of inflammatory cells, the extent of interstitial fibrosis and peribronchial fibrosis, and the numbers of apoptotic cells and of transforming growth factor β-positive cells (37). In a similar mouse model, edaravone improved the survival rate, reduced fibrotic changes and the production of lipid hydroperoxide in BALF and serum, and increased the production of prostaglandin E_2 in BALF (38).

Collectively, these results suggest that edaravone is a potential treatment option for a wide range of lung disorders, including I/R injury, sepsis and fibrosis.

4. Intestinal injury

The mortality rate associated with acute mesenteric artery thromboembolism remains high, despite improvements in diagnostic and therapeutic techniques (39). I/R-related injuries, which occur when a thrombus is removed, result in marked intestinal tissue damage (40). Oxygen free radicals trigger neutrophil infiltration into ischemic intestinal tissues (41). In rats, edaravone reduced I/R-induced small intestine injury; the levels of intraluminal protein and hemoglobin, which are markers of mucosal injury; TBA-reactive substances and tissue-associated MPO activity; protein and mRNA levels of cytokine-induced neutrophil chemoattractant 1 (CINC-1; a member of the IL-8 family; and intestinal erosion and bleeding (42). In that study, CINC-1 protein and *CINC-1* mRNA levels increased with I/R injury and were reduced by treatment with edaravone. Meanwhile, in rabbits with induced acute superior mesenteric artery thromboembolism using autologous fibrin clots, edaravone was reported to prevent bowel infarction, extend survival time, and reduce mucosal damage (41).

The prevalence and incidence rates of Crohn's disease have been increasing in both the United States and in Europe, and there is a strong association between Crohn's disease and cancer of the small bowel (43). In a rat model of acute Crohn's disease, edaravone reduced the ulcer index; histological damage score; and markers of oxidative damage, such as MPO activity and the TBA-reactive substance level, and ameliorated mesenteric indomethacin-induced longitudinal ulcers of the small intestine (44).

5. Liver injury

Acute severe liver injury results from the death of many liver cells and leads to the development of hepatic encephalopathy and severe liver dysfunction (45). Despite major developments in liver support systems and liver transplantation, acute severe liver injury has a high mortality rate (46). It is well known that liver injury can be caused by oxidative stress and subsequent free radical formation (47,48). Recent studies have tested edaravone as a treatment for liver injury in animal models, including liver injury induced by endotoxins (46,49,50), I/R (51-58), carbon tetrachloride (CCl_4) (59,60) and Fas (61).

Edaravone prevented liver injury and improved the survival rate of LPS-treated rats by inhibiting the recruitment of inflammatory cells, the expression of inflammatory cytokines, and by increasing 4-hydroxynonenal-modified proteins in the liver (49). Furthermore, in the same study, edaravone was also reported to inhibit the LPS-induced increases in serum alanine aminotransferase (ALT) levels, in addition to attenuating the mRNA expression of *MIP-2, MCP-1* and *MCP-5*. As a result, edaravone blunted the increase in the number of infiltrating inflammatory cells and the mRNA expression of inflammatory cytokines, such as *TNF-α* and *IL-6*, in the liver. These changes were accompanied by a significant reduction in serum cytokine levels (49).

In another study (50), edaravone prevented LPS-induced liver injury after partial hepatectomy by attenuating oxidative damage and by reducing the production of MDA, CINC, NO, inflammatory cytokines (e.g., TNF-α, IL-2, IL-1β and interferon γ), and inducible nitric oxide synthase (iNOS); these changes were at least partly mediated by inhibition of nuclear factor-κB activation (NF-κB). In this study, edaravone markedly improved the survival rate of LPS-treated rats after hepatectomy and inhibited increases in serum aspartate transaminase (AST) and lactate dehydrogenase (LDH). Histopathological analysis revealed that edaravone also prevented inflammatory changes in the liver, kidney and spleen (50).

Hepatic I/R injury is often encountered following liver transplantation, in hepatic failure after shock, and after liver surgery (62). In rats, edaravone blunted I/R-induced hepatic

dysfunction, hepatic necrosis, hepatic apoptosis, and oxidative stress markers, such as MDA (54). In another study, edaravone blunted I/R-induced worsening of hepatic dysfunction, MDA levels and necrosis, as well as perfusate IL-10 levels in rats (55). Edaravone markedly improved the survival rate of rats following I/R and decreased serum AST, ALT and MPO activity levels, and hepatic *IL-6* mRNA expression (51). Edaravone also ameliorated I/R-induced hepatic dysfunction, lipid peroxidation, and perfusate TNF-α and IL-1β levels in rats (53). Edaravone blunted I/R-induced elevations in serum ALT, serum hyaluronic acid, hepatic *TNF-α* mRNA, serum TNF-α, serum IL-6, Kupffer cell *TNF-α* mRNA, leukocyte infiltration, lipid peroxidation and hepatic free radical levels in rats (52). In another study in rats, edaravone blunted I/R-induced elevations in serum ALT levels, and reduced hepatic congestion, vacuolization, necrosis, lipid peroxidation, tissue monocyte infiltration, neutrophil infiltration, and the mRNA expression of *IL-1β, CINC-2, MIP-2, MCP-1, MIP-1α, MIP-1β*, and intercellular adhesion molecule 1 (*ICAM-1*) (57). Edaravone was also reported to protect against mitochondrial injury by preventing mitochondrial lipid peroxidation, inhibiting decreases in glutathione activity, and improving I/R-induced dysregulation of hepatic energy metabolism in rats (56). Furthermore, edaravone reduced hepatic I/R injury by minimizing hepatic lipid peroxidation, AST leakage, and hepatic *TNF-α* and E-selectin mRNA levels in rats (58). Histologically, edaravone reduced E-selectin immunoreactivity and neutrophil accumulation in rat hepatic sections (58).

CCl_4 is a widely accepted experimental toxin that induces acute hepatic injury and regeneration *in vivo* (59). In rats, edaravone blunted CCl_4-induced increases in serum levels of ALT, LDH, total bilirubin, IL-6, IL-10, and TNF-α; hepatic mRNA expression of *TNF-α, IL4, IL-6*, and *IL-10*; oxidative stress markers such as MDA, 4-hydroxynonenal, and 8-hydroxydeoxyguanosine (8-OHdG); and suppressed fatty degeneration, necrosis, and apoptosis in the liver (59). Edaravone was also reported to blunt CCl_4-induced elevations in serum ALT, LDH, and total bilirubin levels, as well as hepatic steatosis and apoptosis in rats (60). In mice with fulminant hepatic failure, edaravone protected hepatocytes from Fas-induced, mitochondria-dependent apoptosis by regulating mitochondrial Bcl-x_L and Bax expression (61).

An *in vitro* study using primary cultures of rat hepatocytes further revealed that edaravone directly inhibits the induction of iNOS (*NOS2*) gene expression at the level of promoter transactivation and mRNA stabilization in IL-1β-stimulated hepatocytes (63).

6. Pancreatic injury

The annual incidence of pancreatic injury in the United States is reported to be 18 per 100,000 people (64). In a European cross-sectional study, the incidence of acute pancreatitis increased from 12.4 to 15.9 per 100,000 people per year between 1985 and 1995, although the mortality rate remained stable because of advances in treatment (64). Because oxidative stress is observed in various experimental pancreatitis models, the abnormal generation of ROS appears to be independent of the etiology of pancreatitis (65). In an *in vitro* study, edaravone was found to protect isolated islets against cell death induced by 5-250 μmol H_2O_2 in a dose-dependent manner (66). *In vivo*, in a rat model of closed duodenal loop-induced pancreatitis, edaravone tended to reduce ascites volume and inhibit increases in wet pancreatic weight (67). Edaravone also tended to reduce microscopic mucosal damage scores and pancreatic tissue lipid peroxide levels (67). In a rat model of sodium taurocholate-induced pancreatitis, edaravone reduced plasma amylase levels, pancreatic MPO activity, necrosis, edema and inflammatory infiltration (68). Furthermore, edaravone decreased pancreatitis-induced mRNA levels of pro-inflammatory cytokines IL-6 and *TNF-α*. Meanwhile, in another study (69), edaravone was found to protect against multiple-dose streptozotocin-induced diabetes in a dose-dependent manner. In that study, multiple low-dose streptozotocin treatment caused mononuclear cell infiltration in pancreatic islets, which was followed by hyperglycemia and overt diabetes. Notably, edaravone inhibited streptozotocin-induced insulitis by suppressing increases in TBA-reactive substances.

Pancreatic islet transplantation is becoming increasingly widespread for the treatment of type 1 diabetes. However, engraftment survival rates remain suboptimal. One of the causes of poor engraftment following pancreatic islet transplantation is oxidative stress. As a result, only one third of the islet mass is stably engrafted per islet transplantation, and multiple transplants are required to achieve full independence. 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, and decreased the number of TUNEL-positive cells in each islet (70).

Collectively, these results suggest that edaravone may be useful in pancreatic injury to help prevent progressive islet loss, to treat pancreatitis and improve graft survival. Although these effects may be mediated by the antioxidant activities of edaravone, further studies are needed to determine the precise mechanisms of action.

7. Renal injury

Acute renal failure is a dose-limiting factor during cisplatin chemotherapy (71). Accumulating evidence suggests that enhanced peroxidative damage caused by ROS may contribute to the pathogenesis of cisplatin-induced acute renal failure (72). Several studies have demonstrated that edaravone protects against cisplatin nephrotoxicity in rats (72-74). In one study, edaravone reversed elevations in blood urea nitrogen and creatinine and reversed histological changes, such as vacuolation, necrosis, and protein casts, caused by cisplatin (74). In other studies, edaravone reduced cisplatin-induced renal tubular damage, mitochondrial damage, ROS production in mitochondria or proximal tubular cells, and tubular apoptosis in rats (72). Edaravone inhibited cisplatin-induced cytotoxicity in a concentration-dependent manner between 10^{-5}-10^{-3} M). Edaravone also inhibited cisplatin-induced mitochondrial damage, including DNA damage, and prevented renal epithelial cell apoptosis, the occurrence of chronic renal dysfunction, and multiple cyst formation (73). *In vitro*, edaravone attenuated cisplatin-induced cell death, mitochondrial transmembrane potential loss, and ROS production

in murine proximal tubular cells (72), and reversed cisplatin-induced cell injury in porcine tubular cells (71).

Renal I/R injury is a significant complication of renal transplantation and acute renal failure (75-77). In a canine model of I/R injury, edaravone protected renal tubular epithelial cells and vascular endothelial cells, ameliorated renal dysfunction, and reduced MDA, lipid peroxidation, and urinary excretion of 8-OHdG (77). Biopsy specimens showed less tubular cell damage and decreased P-selectin expression in the endothelial cells of treated animals (77). In rats, edaravone improved survival following renal I/R injury (76) and attenuated renal dysfunction, ROS production, lipid peroxidation, and acute tubular necrosis following I/R in acute renal failure (75). The inhibitory effect of edaravone on ROS generation was further verified in a human renal tubule cell line exposed to 0.5 mmol/l hydrogen peroxide for 1 h (75). In rats with puromycin-induced nephrosis, edaravone was also reported to delay or ameliorate 8-OHdG excretion as a measure of *in vivo* oxidative DNA damage (78), and the levels of glomerular TBA-reactive substances (79). Finally, in a rat model of myonephropathic metabolic syndrome and severe hindlimb ischemia, edaravone attenuated neutrophil infiltration, the serum level of soluble ICAM-1, and muscular edema (80).

Collectively, these results suggest that edaravone protects the kidney against I/R injury through its antioxidant activities, particularly during chemotherapy with cisplatin and related drugs. It would also be of interest to determine whether edaravone can be used to improve outcomes following kidney transplantation, which is associated with severe oxidant stress both before and after transplantation (81,82).

8. Bladder injury

There is increasing evidence showing that I/R is a major etiological factor in the progression of bladder dysfunction induced by partial outlet obstruction, and that at least some of the damage is due to the generation of free radicals and the resultant cellular and subcellular membrane peroxidation. In rats, edaravone was reported to protect the contractile responses to field stimulation and carbachol, as well as reduce MDA content following I/R-induced damage to the bladder (83).

Clinically, bladder dysfunction is sustained after acute urinary retention (AUR) (84). In turn, AUR and subsequent catheterization may enhance lipid peroxidation and oxidative DNA damage in the rat bladder. In rats, the administration of edaravone was reported to decrease blood flow in the bladder during urinary retention and catheterization. Edaravone also protected the contractile responses to carbachol and KCl, and reduced MDA, 8-OHdG, and the stress marker heat-shock protein 70 (HSP70; protein and mRNA) following AUR and subsequent catheterization (84).

9. Testicular injury

Testicular torsion is a common urological emergency among infants and adolescents (85). Acute testicular torsion caused by twisting of the spermatic cord and its subsequent release resembles acute I/R injury. The production of free radicals, such as ROS or NO, has been implicated in the pathogenesis of I/R injury. Edaravone reduced the levels of NO_2-NO_3 as a marker of NO production, MDA, 8-OHdG, MPO and HSP70 (protein and mRNA) in a rat testicular torsion model of I/R. Furthermore, edaravone reduced cell swelling, tubular vacuolation, and necrosis in the rat testis following I/R (85). These results suggest that edaravone could be beneficial in the treatment of testicular torsion, although more studies are needed to investigate its efficacy in this setting.

10. Sepsis

Sepsis represents a substantial health care burden. In the United States, sepsis is the second-leading cause of death among non-coronary intensive care unit patients, and the 10th most common cause of death overall according to data from the Centers for Disease Control and Prevention, with the first being heart disease (86). Excessive production of proinflammatory mediators, including cytokines, PAF, oxygen free radicals, and NO, can result in a potentially lethal systemic inflammation associated with the most dramatic pathological sequelae of sepsis, including systemic capillary leakage syndrome, tissue injury, and fatal organ failure (87-90). In a neonatal pig sepsis model, the beneficial effects of edaravone included a reduction in serum free radicals, including NO and total hydroperoxide, and a delay in the elevation of inflammatory mediators, including TNF-α and high-mobility group box 1 (HMGB-1), which in turn delayed progression of sepsis and prolonged survival (91). As described above, edaravone is also beneficial in the treatment of sepsis in individual tissues, particularly the lung, where edaravone prevented lung injury, and attenuated cell activation and the release of pro-inflammatory cytokines induced by LPS (36).

Clearly, more data are needed to better understand the mechanisms of action of edaravone in sepsis given the multiple organ events involved.

11. Toxin exposure

Toxin exposure is also a leading cause of morbidity and mortality. For instance, the herbicide paraquat causes significant damage to multiple organs including the liver, kidney and lung, while antioxidants protect against these deleterious effects (92). Edaravone markedly improved the survival rate of paraquat-treated mice (92). In another animal model of toxin exposure, 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 factors involved in the neurotoxic effects (93). Edaravone has been reported to protect mice against methamphetamine-induced neurotoxicity in the striatum by blocking peroxynitrite production (93). Edaravone also blocked the increase in 3-nitrotyrosine immunoreactivity, a biomarker for ROS generation, and the activation of astrocytes (93).

12. Burns

Recent estimates for the annual incidence of burns and associated medical care use in the United States include 5500 deaths from fire and burns (1991), 51,000 acute hospital admissions for burn injuries (1991-1993, average), and a total of 1.25 million burn injuries (1992) (94). The production of

free radicals, such as superoxide and peroxynitrite, in the early phase of an extensive burn exacerbates many aspects of the injury process, including an increase in microvascular permeability and the production of inflammatory mediators (95). In rats with burn injury, treatment with edaravone significantly reduced the levels of the free radical precursors MDA and xanthine oxidase and their metabolites in serum and tissues compared with untreated rats (95). This suggests that edaravone could be helpful in the clinical treatment of large burns (95).

13. Radiation injury

X-ray-induced cell death occurs via direct and indirect mechanisms. X-rays can directly ionize or excite macromolecules in the cells, leading to cell damage, or X-rays can excite water molecules in cells to produce ROS, which then cause cellular injury (96). Approximately 70% of the biological damage caused by X-rays is caused via the indirect pathway (96). Meanwhile, in MOLT-4 cells, a human T-cell leukemia cell line, edaravone suppressed X-ray-induced apoptosis by inhibiting ROS and p53 expression (96,97). Interestingly, however, a low dose of edaravone was found to sensitize cells to X-ray radiation by activating the p53-dependent apoptotic signaling pathway (97).

14. Hemorrhagic shock

Several experimental studies have revealed that intestinal barrier failure following hemorrhagic shock (HS) or traumatic injury causes bacterial translocation, including the passage of the microorganisms themselves or their components, such as endotoxin or peptidoglycan (98). Oxidative stress induced by ROS is a key mediator in HS-induced vascular hyperpermeability (99). Edaravone was reported to reduce intestinal neutrophil lipid peroxidation and bacterial translocation in a rat HS model (98). Furthermore, edaravone improved the survival rate in a rat model of HS without resuscitation (100).

15. Summary and conclusions

In neurological disease, edaravone principally acts as a free radical scavenger to protect against I/R-induced injury. In this review, we have discussed the possible beneficial effects of edaravone, beyond those associated with I/R injury in the brain following cerebral infarction, in several non-neurological diseases and conditions. The results of the studies discussed in this review point towards multiple mechanisms of action of edaravone, which are attributable at least in part to its anti-oxidant activity, similar to that in neural injury, in addition to several pleiotropic effects. For example, edaravone suppresses the increases in circulating free radical levels and markers of ROS generation associated with I/R injury. Furthermore, edaravone targets numerous intracellular signaling pathways suppressing the release of pro-inflammatory cytokines and the activation/infiltration of inflammatory cells, such as macrophages. Prospective studies are now needed to evaluate the effects of edaravone in clinical settings, and determine whether edaravone is beneficial for diseases and clinical conditions associated with excess oxidative stress and whether edaravone could improve the prognosis of these diseases. We expect that edaravone will be useful for the treatment of diseases and clinical conditions in which oxidative stress plays a key role in their pathogenesis.

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