Clinical Experience of Edaravone in Amyotropic Lateral Sclerosis

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ABSTRACT

Objective. To describe clinical experience with edaravone in ALS over a period of 12 months

Methods. The current study retrospectively investigated characteristics in a group of patients (n=31) with ALS who underwent edaravone treatment. Information including age, gender, race, and site of onset of symptoms were collected for all patients. Adverse events with edaravone therapy was documented where available.

Results. The average age of the patients observed was 62.09 years, with 18 males and 13 females. 18 patients had limb onset, 12 bulbar onset, and 1 diaphragmatic onset. 7 of the 31 patients discontinued treatment at the end of one year. The average age of patients who discontinued edaravone was 65.71 years, of whom which 3 had limb onset, 3 bulbar onset, and 1 diaphragmatic onset. No perceived benefit, port complications, systemic bacteremia, and development of atrial fibrillation were documented as reasons for discontinuation of therapy.

Conclusion. Edaravone is well tolerated in ALS patients at the end of one year. Lack of perceived benefit and port related complications are common reasons for discontinuation of treatment

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder affecting upper and lower motor neurons throughout the nervous system, resulting in gradual paralysis and death in 3-5 years from onset.[1] ALS presents in the 50s to 60s and is the most common neurodegenerative disorder of midlife, with one to two new cases per 100,000 people per year.[1-3] The exact etiology of ALS is unknown, but it is thought to be attributed to the diverse, complex, and combined mechanisms involved in protein, RNA, and cytoskeletal homeostasis which are influenced by both genetic and environmental factors.[1] The presence of oxidative stress has been credited to initiating many of these cellular changes and agreed to be, at least in part, responsible for the onset and progression of ALS.[4-7]

Despite avid research in the field and over 50 randomized controlled trials testing therapies for ALS, treatment is currently limited to only two FDA-approved drugs that may improve survival by merely a few months.[5, 9] Riluzole, approved in 1995, was the first medication to be used for ALS treatment. It is thought elicit its therapeutic effects by suppressing excitatory neurotransmitter release. A second drug, edaravone was approved for ALS treatment in May 2017 and slows ALS progression by acting as an antioxidant to reduce free radical damage.[1] Edaravone was originally marketed in Japan in 2001 as a drug to eliminate lipid peroxides and hydroxyl radicals in order to protect neurons from free radical damage during and acutely after cerebral infarction.[10-13] Mitsubishi Tanabe Pharma Corporation (Tokyo, Japan) then began investigating edaravone as an ALS treatment. The initial randomized controlled trial conducted failed to find statistically significant benefit, but post-hoc analysis and secondary clinical trials demonstrated that edarvone slowed progression of ALS in a subset of patients, evaluated using ALS Functional Rating Scale (ALSFRS-R) scores.[14-16] These Japanese studies led to Edaravone's eventual approval in the United States in May 2017. Criticisms of the trials include the narrow parameters of the study population and the short duration of the trials.[9] Because edaravone is a relatively new drug there is minimal data from U.S. studies on patient outcomes and perspectives, and because the original randomized controlled trials were only conducted over six-month time periods, long-term effects of the drug are essentially unknown.

Edaravone treatment is a time-intensive process for the patient and his or her caregiver(s). The drug is administered via intravenous infusion daily for 14 days, followed by a 14-day break period, and then repeated infinitely until the patient decides to discontinue the medication or dies from his or her neurodegenerative disease. IV infusion requires travel to an infusion center or presence of a home health nurse to administer the medication. Many obstacles face patients receiving edaravone treatment, including insurance approval of the medication, extended distances to infusion centers costing patients valuable time and money, insurance approval of home healthcare services, and guilt surrounding the caregiver's use of time and resources.

Materials and Methods

This study is a retrospective chart review of patients attending a University-based hospital approved by the Institutional Review Board (IRB). The study population includ-

ed patients with ALS who were undergoing care through University of Missouri Health Care.

These patients started on edaravone for management of symptoms due to ALS by the same physician were included in the study. Information including age, gender, race, site of onset of symptoms, ALSFRS-R score, FVC and FEV1/FVC were collected for all of these patients. Adverse events with treatment where available were documented.

The analysis of the data included summarizing patient demographics and changes in FVC in form of descriptive statistical variables including mean, standard deviation, ranges and percentages. Comparison of FVC and ALSFRS-R at different intervals was done by using Wilcoxon signed rank test. All statistical analyses were done using SPSS v22 software (IBM, Armonk, NY).

Results

The entire cohort participating in the study consisted of 31 patients with a mean age of 62.09±8.97 years and 58.04% of the patients had the onset of the disease as the lower limb making it the most common site of origin in our cohort. 54.8% of these patients were found to suffice the El Escorial criteria of definite disease. The demographics and clinical profile of these patients is summarized in Table 1.

Table 1: A summary of the characteristics of patients included in the study.

Average age	62.09±8.97 years
Sex	
Male	18
Female	13
Race	
White	30
African American	1
Onset location	
Lower Limb	18
Bulbar	12
Diaphragm	1
El Escorial Criteria	
Definite	17
Probable	12
Possible	1

Out of the 31 patients enrolled in the study, 7 of patients discontinued the drug. These patients had the average age of 65.71±9.15 years and the reasons of discontinuation of the drug included no perceived benefit by the intervention (28.5%) and port site complications (28.5%) amongst other reasons. The reasons why the drug was discontinued are summarized in Table 2.

Table 2: Reasons for discontinuation of drug amongst the seven patients.

Reason for Discontinuation	Number of Patients who Discontinued
No perceived benefit	2
Atrial fibrillation	1
Port site complications	
Port migration	1
Port site reaction	1
Systemic bacteremia	2

Discussion

Seven of our thirty-one patients, nearly one-quarter, started on edaravone for ALS discontinued treatment by one year of therapy. Reasons for discontinuation included no perceived benefit of treatment by patient and adverse events. Adverse events included port site complications (dermatitis and redness around the port), systemic bacteremia, and atrial fibrillation. We are unable to determine if the adverse events which influenced discontinuation are related to edaravone administration. Of the adverse events recorded in our patients, dermatitis is the only established adverse reaction, and has been reported in 8% of patients.[16-18] Bacteremia is common among patients with frequently accessed medication ports, like those receiving daily edaravone injections 14 days each month.[19] Atrial fibrillation is secondary to a plethora of cardiac and non-cardiac causes and risk factors, and thus is a nonspecific occurrence. Meta-analysis by Lou et al indicated that prevalence of adverse events was similar in patients receiving edaravone and those receiving a placebo.[20] This may suggest that adverse events prompting discontinuation may be more closely linked to patients' predisposing factors.

Of those who discontinued treatment, 28.57% did not determine the drug was effective. We sought to determine reasoning for this perception. This retrospective cohort study found no association between patient characteristics (i.e. sex, race, onset location, El Escorial Criteria diagnosis) and discontinuation status. We have hypothesized several direct and indirect factors which may have contributed to impression of drug ineffectiveness, including difficulty of in-

fusion process, medication cost, and presence of advanced disease. Development of an orally administered form of edaravone may shift perspectives by eliminating infusion process difficulties.[21-22]

Judging therapeutic interventions as clinically or statistically significant can be difficult for complex, mortiferous diseases such as ALS. With lack of serum biomarkers to track disease progress, it is difficult to determine which measures of a disease (i.e. ALSFRS-R, pulmonary function testing, etc.) are most accurate and representative. To enhance analysis of ALS treatments, we propose employing patient opinion of effectiveness as an additional assessment when determining clinical significance because it is a valuable part of treatment success.

Limitations to our study stem from its retrospective nature. We had no control over cohort assignment or data collection. This may have introduced bias into aspects of our data.

In conclusion, when considering edaravone treatment physicians should balance the therapeutic effect, experience of adverse events, and patient perspective of benefit.

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