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RESEARCH ARTICLE

Discussing edaravone with the ALS patient: an ethical framework from a U.S. perspective

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Abstract

The recent approval of edaravone by the United States Food and Drug Administration has generated a mix of hope tempered by reality. The costs of the drug, both monetarily and with regard to intensity of treatment, are high. The benefits, while modest, will be viewed through a very different lens by individuals depending on their goals of care. By virtue of our training and experience, physicians are ideally suited to understand and explain new treatments to our patients. As healthcare providers with a fiduciary responsibility to our patients, we must make sure they are fully informed about both the costs and benefits of non-curative therapies such as edaravone, and be prepared to discuss these in the context of their goals of care and potential impact on quality of life. Respect for our patients' autonomy is critical when discussing these issues, but we should always be guided by the ethical principles of beneficence and non-maleficence.

Keywords: *Amyotrophic lateral sclerosis*, *edaravone*, *ethics*, *quality of life*

Introduction

On May 5, 2017, the United States Food and Drug Administration (FDA) approved edaravone for the treatment of amyotrophic lateral sclerosis (ALS) (1). As the first treatment for ALS to be approved by the FDA in more than 20 years, edaravone has been widely reported by the mainstream media. This has generated significant interest in the drug by ALS patients, their caregivers and the public, resulting in discussions with healthcare providers. Almost immediately after FDA approval, advertisements were published by the mainstream media, noting that "Radicava® (edaravone) is the first FDA-approved treatment option for amyotrophic lateral sclerosis (ALS) in more than 20 years." A spokesperson for The ALS Association noted "a great deal of excitement" over the drug's approval, and added that "…this approval has brought true hope to this community." (2) The enthusiasm appears to have extended to the FDA itself. According to Eric Bastings, MD, deputy director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research, "after learning about the use of edaravone to treat ALS in Japan, we rapidly engaged with the drug developer about filing a marketing application in the United States" (1).

For those of us (ZS) who have spent much of their professional careers caring for individuals with this devastating disease and participating in clinical trials and other research to improve the lives and the life expectancies of people with ALS, the identification of a new treatment is indeed welcome news. However, the possibility of an additional treatment option raises a number of questions, particularly when that treatment is neither curative nor stabilizing. Should the use of edaravone be encouraged in all patients? Should it be encouraged in some patients? The fiduciary responsibility of physicians to our patients, and by extension to their caregivers and other members of the ALS community, is best met if we take a step back and conduct our discussions of edaravone therapy with thoughtful consideration of the costs, benefits, implications for quality of life (QOL), and interplay of these factors

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within the framework of the core ethical principles that guide the provision of clinical care.

Historical background

In December 1995, the FDA approved riluzole, a sodium channel blocker and indirect glutamate antagonist that produced a modest survival benefit in ALS patients (3–5). Approval in Europe and Japan followed in 1996 and 1998, respectively. As multiple drugs targeting heterogeneous pathways proved successful in ALS animal models but failed in human clinical trials in subsequent years, riluzole remained the only FDA-approved drug for ALS. In 2014, a report was published of a phase III trial in patients with ALS of edaravone, a free-radical scavenger used to treat acute ischemic stroke in Japan. There was no significant difference between the placebo and treatment groups with regard to the rate of decline of the ALS Functional Rating Scale-Revised (ALSFRS-R) score (6), but *post-hoc* analysis identified a subgroup that demonstrated better outcome, defined by slower rate of decline in the ALSFRS-R. This Efficacy-Expected Subpopulation, the dpEESP2y subgroup, had scores of 2 or higher on all 12 items of the ALSFRS-R, forced vital capacity (FVC) of at least 80% of predicted, disease duration of 2 years or less, and definite or probable ALS by El Escorial revised criteria (7). A randomized, placebo-controlled Phase III study then prospectively enrolled patients who fulfilled criteria for the dpEESP2y subpopulation. Results were reported in 2017 (8). Over a 24-week period, the edaravone group demonstrated a smaller decline in the ALSFRS-R than the control group (5.01 vs. 7.50 points). The declines in the ALS Assessment Questionnaire (ALSAQ-40), a health-related QOL measure, and the Modified Norris Scale, which measures extremity and bulbar function, were also smaller in the edaravone group. There were no differences between the edaravone and control groups in FVC, grip strength or pinch strength. The adverse drug effects were minimal and occurred with similar frequencies across both groups.

It would appear from the description above that edaravone is beneficial and the risks small. What are the ethical concerns? One could argue that ALS is a devastating disease, and a low-risk therapy that potentially offers some benefit is in the patient's best interests. A more sophisticated perspective comes from a better understanding of the financial and personal costs, and a weighing of benefits vs. costs when considering the overall impact on QOL.

Ethical principles

The implications of offering edaravone to ALS patients in the US should be viewed in the context of the core ethical principles of autonomy, beneficence (doing good), and non-maleficence (avoiding harm) that guide the treatment of all patients (9). Autonomy refers to the right of the patient to make an informed and voluntary decision about his or her healthcare based on personal values, without coercion (9). In this sense, a competent adult patient is autonomous, and ultimately has the right to make decisions with which his or her physician may or may not agree. Knowing this, it is the duty of the physician to provide such a patient with information and guidance so as to maximize the possibility of benefit (beneficence) and minimize the risk of harm (maleficence). Intrinsic to this is the principle of informed consent, which guides all treatment interactions between patients and their healthcare providers. As an integral part of this, physicians must candidly explain not only benefits, but risks (costs) as well. Because cognitive impairment may affect as many as half of individuals with ALS, and as many as 15% may meet criteria for frontotemporal dementia (10), it is important for the treating physician to judge the capacity of the ALS patient for decision-making, and to ensure that a legally-authorized representative is available for discussions of treatment when capacity is compromised.

Benefits of edaravone

Given the general level of enthusiasm in the lay press and among advocacy groups for approval of this new drug, patients may not be aware that the benefits of edaravone are modest, even in the selected subgroup of the pivotal study. This does not reflect lack of candor on the part of those who performed the study (8). The authors explicitly noted that efficacy was substantiated only for those patients investigated in the study, and that the question of whether edaravone might be safe and effective in a broader population of patients with ALS would require further study (8). However, most patients do not have the expertise to read and critically evaluate original medical and scientific literature, and may mistakenly believe that a drug *approved* for all patients with ALS must be *effective* for all patients with that diagnosis. The approval by the FDA may give patients a false sense of security about the efficacy of edaravone because they may misperceive an approved drug from a "successful" trial as one that improves strength or function. To put the modest results in perspective, as pointed out by the European Network for the Cure of ALS (ENCALS), most patients with ALS decline by about 5.6 points on the ALSFRS-R over 6 months, and patients taking edaravone lost 5.1 points on the ALSFRS-R scale versus 7.5 on placebo over 6 months (11). Clarification of these points is critical.

Edaravone has not yet been approved in Europe. ENCALS recently published a statement on

edaravone expressing many of the concerns that are rarely emphasized in the media but are important for patients to understand and critical for the treating physician to communicate (11). Among these are the following: (1) the effects on muscle strength and respiratory function are incompletely understood; (2) the effect on survival is not known; (3) efficacy appears to be limited to those patients who meet the inclusion and exclusion criteria of the pivotal study used by the FDA for approval; (4) the benefits, if any, beyond 6 months are not known; and (5) the benefits for non-Asians are not clear. In regard to this last point, there is literature indicating that clinical practice, demographics and progression of disease appear to be similar between patients with ALS in Japan and those in the US and Europe (12). There are also data demonstrating that pharmacokinetic profiles of edaravone appear to be similar in Japanese and Caucasian populations (13). Nonetheless, broad clinical trials of patients with diverse ethnicity are lacking. Relevant to this, the genetic contributors to ALS, when known, appear to differ between ethnic groups (14), and the implications of these for drug therapies are unknown, Based on their concerns, ENCALS recommended that "an extended clinical trial with at least 12 months follow up, including analysis of effects on survival, is indicated to resolve these questions, and to ensure that appropriately selected patients with ALS have maximum opportunities to avail themselves of a potentially beneficial therapeutic agent" (11).

Risks/costs of edaravone

The medical and biological risks of edaravone appear to be low, as previously noted. However, data are limited, as the pivotal trial was small, and the duration limited to 6 months. The indwelling intravenous line which will need to be placed in patients receiving edaravone is associated with a risk of thrombophlebitis and infection, which is of particular concern because this patient population at baseline has a far higher incidence of venous thromboembolism than that of the general population (15,16), and because the duration of treatment to which patients will be exposed is unknown, and may be long.

When discussing therapies with patients, financial cost and potential negative impact on QOL must be considered if the physician is to maximize beneficence and to "do no harm." A report by the Committee on Health Literacy, supported by the Institute of Medicine of the National Academies, noted that public comprehension of medical risk is low (17). Superimposed upon this, the perception of efficacy and risk-benefit balance of edaravone may be impaired by the desperation of having a terminal disease for which only one other FDA-approved drug exists. Terminally ill patients often over-estimate the benefits and under-estimate the burdens of experimental therapy, and those with a life expectancy of less than 6 months frequently have impaired decision-making capacity (18). Although edaravone is not experimental therapy, physicians should still consider these factors, which affect decision-making capacity and put their patients in a vulnerable position, when discussing a newly-released therapy with their patients.

Treatment with edaravone is intensive. The drug is given intravenously for 14 days, followed by a period of no treatment for 14 days. After this, it is administered in 28-day cycles, each consisting of infusions for 10 of 14 days followed by periods of 14 days off drug. Patients who opt for treatment must understand that nearly half of their days will be ones on which they receive a 60-minute intravenous infusion.

The financial cost of edaravone is substantial. At approximately $1000 per infusion, this adds up to more than $140,000 per year per person (19). Although the FDA has approved the drug, commercial insurers are independently making their coverage determinations, and individual policies by each insurer may vary in their coverage as well. Some insurance companies are limiting coverage to those patients who meet inclusion criteria of the trial that led to FDA approval. Often unclear at this early stage of experience with edaravone is whether coverage will be provided for longer than 6 months, or will continue for those patients who are receiving edaravone but whose disease progression places them outside of the original inclusion criteria. Other factors such as the placement of an indwelling intravenous line, the administration of home-based vs. center-based infusions, the co-payment that may be required with an individual insurance policy, and the manufacturer's cost-sharing program for patients without insurance or with very high out-of-pocket costs, will determine whether edaravone is a financial burden for individuals.

Balancing benefits and risks: assessing the goals of care

Assuming that edaravone reduces the rate of disease progression, and assuming that costs can be assessed, or at least estimated, as summarized above, patients and healthcare providers are confronted with the challenge of determining whether the benefits outweigh the costs. Patients with ALS express varied goals. For some, prolongation of life is paramount. This may reflect a desire to witness a milestone in their life or in that of a family member, such as the birth or graduation or wedding of a child or grandchild. Alternatively, it may reflect a belief in the sanctity of life. For others, comfort is most important. For still others, survival is desired until specific functions are lost, such as verbal

communication. These are just a few examples of goals of care, which are naturally highly individualized and patient-driven. When discussing a new therapy such as edaravone, identification of such goals will often guide the discussion. For many patients, a key consideration will be the impact on QOL.

Quality of life

Does edaravone positively impact QOL? There was a favorable effect on the ALSAQ-40, a health-related QOL instrument, in the study that led to FDA approval (8). However, QOL is a complex and nuanced concept. Health-related QOL measures, including the ALSAQ-40, are heavily weighted toward physical function and generally will rise and fall in parallel with it (20–22). In contrast, global QOL is determined not only by physical health but also by psychological, existential, and support factors. A variety of non-medical factors such as family, friends, finances, job, and religion or spirituality, play roles as well (23,24). The patient's QOL is often rated higher by the affected individual than it is by others, including caregivers and healthcare providers (25–28). Importantly, global QOL in patients with ALS does not correlate with strength or physical function (23,29). Maintenance of QOL in those with life-threatening disorders has been attributed to a response shift (frame shift), whereby the patient adjusts expectations to match reality, so that those factors most important to maintaining QOL shift from those requiring physical abilities to those based on existential, interpersonal, and other nonphysical factors (30–33). If patients have begun this process of shifting their expectations and a new drug such as edaravone is released, a patient's mistaken hope for better strength and a cure may impair the adaptation that occurs during response shift. It is important for each clinician to ensure that a patient's expectations of a new therapy reflect reality so that the introduction of this treatment does not paradoxically lower QOL.

Physicians should thoroughly review the various costs and benefits discussed earlier, because non-health related factors associated with edaravone use may impact QOL substantially. Such factors could include, among others, financial costs of the drug and infusion, the need to reduce visits with family or friends to travel to an infusion center, and the need to curtail meaningful work activities to begin daily infusions. Physical factors such as fatigue from daily infusions or daily travel to an infusion center may play a role in reducing QOL as well. Alternatively, if the infusions are concordant with a patient's goals, they may positively impact QOL via the existential domain by providing meaning. Examples of this are the ability to be in a less weakened state at a seminal event in a family member's life, or the extension of ability to communicate effectively.

Physicians must be mindful of the fact that not all patients with ALS have a successful response shift, and some suffer greatly. Although QOL, on average, remains stable during the ALS trajectory, the psychological morbidity of some patients is substantial, and in aggregate the psychological well-being of those with ALS is poorer than that of the overall population (34). Depression, hopelessness, and anxiety are associated with poor QOL (35–38). If an individual's psychological health and QOL are poor, might edaravone prolong this? Detailed discussions of goals of care and QOL are essential to helping patients weigh the benefits vs. costs of therapy in order to arrive at a plan that facilitates their goals of care and optimizes their QOL.

Concluding thoughts

As physicians, we are patient advocates. The patient–doctor relationship is a complex one, always incorporating respect for autonomy, and being guided by the principles of beneficence and non-maleficence. Individuals with ALS have a devastating and frightening disease that may strain family ties, pose challenges even for those with well-developed coping skills, and eventually control much of what occurs, and how it occurs, throughout a patient's days and nights. A physician who takes time to understand the clinical trials that lead to drug approval, and who can compassionately frame the medical facts in the context of the patient's needs and goals, is an invaluable resource to patients. The landscape of medical research is rapidly evolving, and eventually clinical trials may lead to therapies that result in stabilization, improvement, or even cure for our ALS patients. Patient subgroups may be selected on the basis of genetics and pathogenesis rather than clinical parameters. In the near future, however, approved treatments for ALS are more likely to have limited benefits, such as those seen with riluzole and edaravone, and to be accompanied by additional risks and costs for our patients. Thus, the therapeutic landscape likely will become more complicated by additional but modestly effective drugs. It is our responsibility as physicians to ensure that our discussions with our ALS patients concerning their treatment decisions about edaravone and future therapies are made in accordance with the ethical principles outlined here, always aimed at facilitating the best QOL as viewed by the patient.

Declaration of interest

Dr. Yeo reports no conflict of interest.

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