Multidisciplinary Care for the Patient with Amyotrophic Lateral Sclerosis

LORA L. CLAWSON, MSN, CRNP
ASSISTANT PROFESSOR NEUROLOGY
DIRECTOR OF ALS CLINICAL CARE & CLINICAL RESEARCH
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
Lora L. Clawson discloses no actual or potential conflict of interest related to this program
Objectives

- Meeting the unique needs of the ALS patient and their family
  - Demographic information
  - Criteria for diagnosis
  - How ALS affects individuals
  - Theories, trials and future directions
  - Expectations of Edaravone/Radicava® & Riluzole/Rilutek®
  - Clinical management, ongoing monitoring & research
  - Role of ALS Multidisciplinary Clinical Team including Home Infusion & Home Care Companies in Clinical Care
  - Community Resources/Non-Profit Organizations
ALS – A NEW ERA

- 1874: JM Charcot discusses the features of ALS
- 1990s: rapid increase in understanding of the pathophysiology
- 1995: Riluzole (Rilutek®) is the first drug approved by the FDA
  - Double-blind, placebo-controlled clinical trial
  - Inhibits glutamate release
- 2017: Edaravone (Radicava®) is the second drug approved by the FDA
  - Double-blind, placebo-controlled clinical trial
  - Anti-oxidant
ALS DEFINITION

- World Federation of Neurology El Escorial Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis
  - Upper motor neuron loss
  - Lower motor neuron loss
  - Progression
  - Absence of other disease processes
  - Levels of diagnostic certainty:
    - Definite, Probable, Possible
ALS DEMOGRAPHICS

- Age at onset of symptoms
  - Full adult age range
  - Mean age: 55 years
- Gender
  - 1.5:1 males: females
- Incidence
  - 1-2 per 100,000
- Prevalence
  - 6 per 100,000
ALS PATIENT POPULATION

First Clinical Presentation
- 75% Limb onset
  - Speech, swallowing, and breathing functions
- 25% Bulbar onset

ALS Age Range
- Median age: 54
- 20-90 years old

ALS Survival Time Range
- Patients can survive a few months to > 20 years
- Typical: 2-5 years

Familial ALS Cases
- 60% of familial ALS cases are tied to a specific genetic defect
- 5-10% of patients have a family history of ALS

Source: Cell, 2017; Volume 171: p. 725
TYPES OF MOTOR NEURON DISEASE

- Progressive Muscular Atrophy (PMA)
- Spinal Muscular Atrophy (SMA)
  - Lower Motor Neuron
- Primary Lateral Sclerosis (PLS)
  - Upper Motor Neuron
- Amyotrophic Lateral Sclerosis (ALS)
  - Upper and Lower Motor Neuron
- Progressive Bulbar Palsy (PBP)
  - Bulbar onset of ALS
TYPES OF ALS

- Sporadic (SALS)
  - No family history
- Familial (FALS)
  - SOD 1 gene mutation – autosomal dominant
  - C9orf72 gene mutation – ALS/FTD
ALS ANATOMY

Overview of Motor System

- Central – cerebral cortex, basal ganglia, thalamus, cerebellum, brain stem, spinal cord
- Peripheral – alpha motor neurons, neuromuscular junction, muscles
How movements are performed

- The thought
- The motor program
- Target identification, planning of action
- Activation of appropriate UMN
- Activation of appropriate LMN
- Desired movement executed
- (Feedback and coordination functions normal)
ALS PHYSIOLOGY

- Motor program
  - Strategy for desired movement
- Activation of Motor Cortex (UMN)
  - Corticobulbar neurons
  - Corticospinal neurons
- Motor Unit Recruitment (LMN)
  - Generation of sufficient strength
  - Desired movement accomplished
ALS PATHOLOGY

- Death of Upper Motor Neurons
  - Loss of Betz cells from motor cortex
  - Degeneration of lateral corticospinal tract – “lateral sclerosis”

- Death of Lower Motor Neurons
  - Loss of anterior horn cells
  - Fiber type grouping in muscle – “amyotrophy”
ALS PATHOPHYSIOLOGY

- Compensatory collateral reinnervation in muscle
  - Surviving motor neurons sprout new branches to reinnervate widowed muscle fibers
  - Preserves muscle strength in early phase
  - Reinnervation fails to continue to compensate when >50% of LMN’s die
  - Clinical weakness appears at this point
ALS DIAGNOSIS

Patient History

- Diffuse asymmetric weakness and atrophy of voluntary muscles
- Steady progression
- Fatigue, cramps, fasciculations, weight loss
- Ease of laughing, crying or yawning
- Occasional sensory symptoms
ALS DIAGNOSIS

- Examination: Lower Motor Neurons
  - Asymmetric atrophy and weakness in a diffuse pattern
    - Diffuse fasciculations and cramps
  - EMG findings: ongoing diffuse acute & chronic denervation

- Examination: Upper Motor Neurons
  - Pathologic tendon reflexes (spread) ; Clonus
  - Spasticity to passive manipulation
  - Extensor plantar (Babinski) response ( in 50% - presents late)
  - Associated signs – ease of laughing, crying or yawning
ALS DIAGNOSIS

- **Uninvolved**
  - Bowel and bladder function (incontinence)
  - Special senses
  - Ocular function
  - Organ function

- **Occasionally Involved**
  - Pain
  - Mental status
  - Sensory system
ALS DIAGNOSIS

- Electromyographic (EMG) Findings
  - Ongoing denervation and reinnervation in a diffuse pattern
  - Normal motor and sensory nerve conduction velocities
- Muscle biopsy (r/o myopathies)
- Magnetic Resonance Imaging (MRI) (r/o lesions)
- Cerebrospinal Fluids (r/o MS, malignancies)
- Routine laboratory testing
ALS CLINICAL FEATURES

- **Bulbar**
  - Impaired ability to: handle saliva, chew/swallow, speak, nutrition

- **Neck Weakness**
  - Impaired ability to hold head erect, saliva, chew/swallow, walk

- **Upper Extremity Weakness**
  - Distal, proximal, Impaired ability to perform activities of daily living

- **Trunk Weakness**
  - Impaired ability to turn in bed, stand erect, walk, breath

- **Lower Extremity Weakness**
  - Distal, proximal, impaired ability to rise from chair, falls, walk, transfer, dress

- **Respiratory Muscle Weakness**
  - Impaired ability to cough, breath, speak, walk
ALS CLINICAL FEATURES

- General
  - Fatigue
  - Cramps
  - Fasciculations
  - Spasticity
  - Ease of laughing, crying or yawning
  - Musculoskeletal aches and pains
ALS CLINICAL FEATURES

Functions Rarely Affect
- Cognitive
- Sensory
- Ocular
- Bowel and Bladder

Functions Not Affected
- Smooth and cardiac muscle
- Internal organ (function)
- Sexual
ALS CLINICAL FEATURES

- Prognosis
  - 50% die within 2-5 years of symptom onset
  - 10-25% of patients are alive at 10-15 years after symptom onset
  - Late onset associated with rapid progression
  - Rate of progression generally constant within an individual
  - Rate of progression may plateau in late stages
PATHOGENESIS OF ALS:
CURRENT RESEARCH THEORIES

- **Excitotoxic Hypothesis**
  - Excess glutamate, transporter defect

- **Oxidative Stress/Free Radical Damage**
  - Cu/Zn (SOD1 gene mutation) on chromosome 21

- **Autoimmune Hypothesis**
  - Calcium channels (L-type) antibodies

- **Cytoskeletal Abnormalities**
  - Neurofilament accumulations
POSSIBLE THERAPIES & FUTURE DIRECTION FOR RESEARCH

- Antiexcitotoxic agents
- Antioxidants
- Immunosuppressants
- Neurotrophic Factors
- Stem Cell Therapy
- Gene Transfer Therapy
- Combination therapy
PHILOSOPHY OF CLINICAL TRIAL PARTICIPATION

www.clinicaltrials.gov

“A valid, controlled clinical trial is a real expression of hope.”

Clawson, Rothstein & Kuncl (1993)
PHILOSOPHY OF MEDICAL TREATMENT

“There is a great deal that can be done to treat the symptoms of ALS, to improve the quality of life of a patient, and to help caregivers and the family cope with the disease.”

Mitsumoto & Norris (1994)
CLINICAL CARE OF ALS – OVERVIEW

- Psychosocial Issues
- Functional Disabilities
- Dysarthria
- Dysphagia
- Respiratory Insufficiency & Failure
- Symptom Management
- Terminal Care
ALSFRS-R
Revised ALS Functional Rating Scale

- Validated Questionaire to Evaluate Functional Decline – assessing bulbar, fine motor, gross motor, and respiratory functions
- Assessing physical functioning carrying out activities of daily living
- Each task is rated on a five-point scale for
- 0 = can not perform task to 4 = normal stability
- Individual item scores are summed to produce a reported score of between 0=worst to 48=best
PSYCHOSOCIAL ISSUES

- Assess coping mechanisms and problem solving skills
- Promote support group participation by patient and family
- Encourage participation in valid clinical trials
- Encourage continued lifestyle – hobbies, social interaction
- Promote use of ALS informational sites on the internet
FUNCTIONAL DISABILITIES

- Assess muscle strength, endurance, gait and balance
- Teach stretching and exercise program
- Teach energy conservation and compensatory techniques
- Discuss barriers to independence
- Encourage communication with other patients to learn about existing solutions
- Familiarize patient with adaptive aids and equipment
DYSARTHRIA

- Assess speech volume, quality, time of day affected
- Discuss relaxation, positioning, compensatory techniques
- Utilize simple communication tools
- Encourage concise phrasing, exaggerated articulation
- Recommend use of augmentative communication device
COMMUNICATION AIDS

- Note pad
- Magic slate – Boogie Board
- Call device (dinner bell, clicker, intercom system, Speak and Spell)
- Letterboards (ETRAN, letter cuff [alphabet list worn on forearm])
- Hand-held computers with print-out device
- IPHONE, IPAD, Laptop computer – Applications - Proloquo2go
- Speech Amplifier Devices
- Speech Generating Devices – Tobii-Dynavox
  - Specific software capabilities adapted to patient needs
  - Voice synthesizer
  - Switches adaptable to head movement, eye blink or suck/blow
DYSPHAGIA

- Assess nutritional state – weight, swallowing study
- Instruct in swallowing techniques – chin tuck, concentrate/minimize distractions
- EMST – expiratory muscle strength training; Heimlich maneuver
- 5-6 small portion meals per day, small bite size pieces, avoid problem textures and consistencies – avoid sweet/sour (increase secretions) avoid milk products (thick stringy secretions)
- Adequate calories, fiber and fluid intake
- Alternative feeding devices – GT, PEG, percutaneous gastrojejunostomy
FEEDING TUBE DECISION

- Educate patient and family regarding ALS and prognosis
- Encourage a thoughtful decision, not an emotional one
- Emphasis on nutrition & hydration support
- Discuss type of feeding tubes – pros and cons
- Discuss advanced directives
- Seek advice from experienced individuals
RESPIRATORY INSUFFICIENCY & FAILURE

- Assessment of respiratory state – FVC, strength of cough and voice
- Vaccinate for flu and pneumovac
- Instruct in energy conservation, breathing exercises
- Instruct in chest PT, assistive cough techniques
- Discuss assistive breathing devices, secretion mobility devices, tracheostomy, long term ventilation, advanced directives, hospice
VENTILATOR DECISION

- Educate patient and family
- Encourage a thoughtful decision – discuss the long-term impact
- Discuss all alternatives – pros and cons
- Assess resource availability
- Discuss advanced directives
- Seek advice from experienced individuals
SYMPTOM MANAGEMENT I

- Sialorrhea: Robinul, Elavil, Levsin, Sal-Tropine, suction machine
- Xerostomia: Humibid, bedside humidification, chin strap at night
- Cramps: Quinine sulfate, Baclofen, Valium, stretching exercises
- Constipation: adequate fluid & fiber intake, laxatives, herbal teas
- Phlegm: adequate hydration, avoidance of milk products, chest PT
- Cough: honey & lemon juice, Robitussin, codeine, Atrovent inhaler, Proventil/saline in nebulizer, chest PT, cough assist device
SYMPTOM MANAGEMENT II

- Depression: Zoloft, Paxil, patient & family counseling
- Emotional lability: Nuedexta, Elavil, patient & family education
- Fatigue: Mestinon, Modafinil, energy conservation techniques
- Dyspnea: Relaxation & breathing exercises, BiPAP, Nebulizer treatments, morphine
- Insomnia: Benadryl, Ambien, Restoril, Ativan, Trazadone, positioning, adequate room ventilation, meditation, relaxation exercises, sleep study evaluation
- Skin Breakdown: keep skin clean & dry, pressure relief, frequent repositioning, Jay cushion for wheelchair, floatation mattress for hospital bed
PALLIATIVE CARE/HOSPICE CARE

- Patient and family support & education
- Referral to hospice
- Dignity and comfort
- Symptom management
- Research participation - Autopsy and tissue donation
- Participation in mourning process
Riluzole - RILUTEK®

- Clinical trial results – first drug shown to have an effect in ALS
- Mechanism of action – inhibitory effect on glutamate release
- Dosage and Administration – 50mg PO BID 1 hour before meals or 2 hours after meals; statistically significant improved survival
- Storage & Handling – white capsule shaped film coated capsules stored at 20-25 degree C/68-77 degree F; protect from bright light
- Adverse reactions – increased ALT (SGPT)/AST (SGOT); asthenia; nausea; vomiting; vertigo; somnolence; paresthesia
- Contraindications – history of hypersensitivity to riluzole; liver sensitivity or toxicity
- Patient Education – AST/ALT – baseline/30/60/90 days; yellowing of whites of eyes; fever; respiratory symptoms
KAPLAN-MEIER SURVIVAL CURVE
STUDY 216 – STUDY I

Source: http://products.sanofi.us/rilutek/rilutek.pdf
KAPLAN-MEIER SURVIVAL CURVE
STUDY 301 – STUDY II

Source: http://products.sanofi.us/rilutek/rilutek.pdf
Edaravone - RADICAVA®

- Clinical trial results – first drug approved for ALS in 22 years
- Mechanism of action – antioxidant
- Dosing & Administration - Regimen is in cycles – 30mg/100ml (0.3mg/ml) single dose bag – 2 bags to a package – clear colorless sterile solution
  - Initial treatment cycle - 60mg IV QD for first 14 days; then 14 days with no drug
  - Subsequent cycles - 60mg IV for 10 out of 14 days; then 14 days with no drug
- Storage & Handling – store at 25 degree C/77 degree F – excursions permitted from 15-30 degree C/59-86 degree F; protect from light; Store in overwrapped package to protect from oxygen degradation until time of use. O2 indicator will turn blue/purple if O2 has exceeded acceptable levels. Once overwrap package is opened use within 24 hours.
- Adverse reactions – Bruising, gait disturbance, headache, dermatitis
- Contraindications – Hypersensitivity Reactions; Sulfite Allergic Reactions; Contains sodium bisulfite
- Patient Education – PICC/PORT Access line care & maintenance; IV Administration procedure; side effects – hives/itching; trouble breathing/wheezing; trouble swallowing; dizziness; swelling of lips/tongue/face; trouble walking.
HISTORY OF RADICAVA®
DEVELOPMENT

Late 1980s
Developed as a free radical scavenger for stroke. Never approved for stroke in USA or Europe.

1990

1990s-2011
Repeated clinical failure in prior ALS trials (> 50 trials)

1995
FDA approval of Riluzole

2000

2001
Marketed by Mitsubishi Tanabe for stroke in Japan. It is now generic.

2005

2010

2011
Mitsubishi starts ALS trials

2015

2017
Approved for ALS in Japan

Source: Cell, 2017; Volume 171: p. 725
Mean Change in ALSFRS-R Score

Change in ALSFRS-R Score from Baseline

Source: https://www.radicava.com/hcp/efficacy-and-safety/#effect-on-physical-function
SURVIVAL RATE WITH RADICAVA®

Source: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 18: 55-63
RADICAVA® CHALLENGES

- M T PHARMA – distributor – manufactured in Japan NOT US
- Third Party: Searchlight Enrollment Company
- Home Infusion vs. Outpatient Infusion
  - Home: Agreement may not exist
  - Outpatient: Agreement may not exist; Most require patients to be independent; provider needs to have privileges at site
- Current Clinic Visits for all Patients to update/monitor clinical care & educate on Radicava prescribing process & expectations
- Method of Infusion: PIV vs. Midline vs. Central line/PICC or PORT
- Staffing – Neurology Clinic, Insurance companies, Home Care/Infusion companies
- Some insurances will only approve for patients who mimic phase II study participants (FVC > 80%, Onset < 2yrs, ALSFRS-R > 40, etc.)
MULTIDISCIPLINARY HEALTH CARE
TEAM OF SPECIALISTS

- Physician
- Nurse Clinician
- Psychologists
- Social Worker
- Home Health Care
- Home Care Infusion Center
- Palliative Care/Hospice Care
- Physical Therapist
- Occupational Therapist
- Respiratory Therapist
- Nutritionist
- Speech-Language Specialist
Collaboration with Home Care/Home Infusion Companies with Multidisciplinary Clinical Care Team

- Home Safety Evaluation
- Home Physical Therapy
- Home Occupational Therapy
- Home Speech/Swallowing Therapy
- Home Social Worker
- Home Respiratory Therapist

- Radicava – PICC/PORT care – patient education / demonstration – ongoing monitoring & assessments
- Enteral Nutrition
- Respiratory Equipment & monitoring – Bipap, Compliance use data, Cough assist device, suction machine, Vest
- Durable Medical Equipment – cane, rollator walker, handrails/safety bars, wheelchairs manual/power, patient lifting devices, hospital bed, recliner lift chair, stairglide
- Accessible Van & ramps
NON-PROFIT ORGANIZATIONS INFORMATION & REFERRAL

- Amyotrophic Lateral Sclerosis Association
  - Phone: (800) 782-4747
  - Email: alsinfo@alsa-national.org
  - Website: www.alsa.org

- Muscular Dystrophy Association
  - Phone: (800) 572-1717
  - Email: mda@mdausa.org
  - Website: www.mda.org

- Amyotrophic Lateral Sclerosis Society of Canada
  - Phone: (800) 267-4257
  - Website: www.als.ca

- Muscular Dystrophy Canada
  - Phone: (416) 488-0030
  - Email: info@muscle.ca
  - Website: www.muscle.ca
SUMMARY

- Enhanced your core knowledge and skills to effectively manage ALS patients throughout their disease process.

- Provided an overview of current treatment regimens, complimentary therapies, and methods to identify and treat symptoms associated with disease progression.
Questions?