Strategies to Manage Neuropathy after Transplant

Celebrating a Second Chance at Life
Survivorship Symposium

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Introduction

• What is peripheral neuropathy?
• What are the different types of neuropathy experienced post-transplant?
• Common symptoms of peripheral and autonomic neuropathy
• Causes of neuropathy during/after transplant
• How neuropathies are diagnosed
• Therapies to help manage symptoms
• Which providers manage neuropathy and how to find one
Neuropathy: Definition

• Damage to the peripheral nerves

• Typically affects the longest nerves first
  ie. “stocking glove pattern”

• Why is that?
The Different Types of Neuropathy

• Peripheral neuropathy
• Autonomic neuropathy
• Mononeuropathy
• Plexopathy
• Optic neuropathy
Peripheral Neuropathy

- **Symptoms**: numbness/tingling/burning starting in toes +/- imbalance & weakness
- Rare in stem cell transplant (1-5%)
- Most patients have a mild sensory predominant form
  - Rarely (~0.4%), patients have an immune mediated severe form with weakness

Dowling, 2018
Ruzhansky, 2015
Autonomic Neuropathy

• Nerves that control involuntary bodily functions
  • Blood pressure and heart rate regulation
  • Bowel and bladder function
  • Sexual function
  • Visual and sweating function

• Rare after HSCT

• *Can occur in setting of a plasma cell disorders (AL amyloidosis>multiple myeloma) vs chemotherapy
Mononeuropathies

- Mono = when a single nerve is injured
  - Usually due to compression
- Carpal tunnel syndrome is the #1 common form
- Ulnar neuropathy #2 common form
- Causes episodic focal numbness/tingling, worse at night or with activity
- Good treatment options (more later)
Plexopathy

- Inflammation of a plexus (network) of nerves
  - Brachial plexus: upper arm
  - Lumbosacral plexus: pelvis
- Occurs earlier (<6 months) after transplant
- Symptoms: pain followed by weakness and numbness
- Theory: this represents an abnormal immune system
- Rare: 0.3-1% have immune neuropathies

Ren, 2019; Li, 2016
Optic Neuropathy

• Damage to the optic nerve (carries visual information from eye to brain)

• Most commonly due to treatment (tacrolimus or cyclosporine), rarely as complication of transplant

• Symptoms:
  • eye pain
  • reduced color vision
  • reduced vision
Symptoms of Peripheral Neuropathy

• **Small fiber neuropathy**: pain, burning, tingling
  - (more common, early in course)

• **Autonomic neuropathy**

• **Large fiber neuropathy**: numbness

• **Motor neuropathy**: weakness

Often a combination
Symptoms of Autonomic Neuropathy

- Decreased sweating
- Difficulty adjusting to the dark
- Lightheadedness with standing (orthostatic hypotension)
- Digestive issues (diarrhea, constipation, poor appetite)
- Urinary issues (retention, frequency, urgency)
- Sexual dysfunction

“Fight or flight, rest and digest”

http://animalia-life.club/animalia-view.html
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Causes of Neuropathy Before Transplant

• Neuropathy is a common complication of hematologic malignancies
  • Multiple myeloma: 15-20% have neuropathy
  • AL amyloidosis: ~40% have neuropathy
• Neuropathy is also common with chemotherapy
Chemotherapy-Induced Peripheral Neuropathy

- **Bortezomib (Velcade):** 35-50% develop neuropathy
  - Usually occurs within the first few courses, plateau ~ cycle 5
  - Painful!!!

- **Thalidomide:** 23-50% reported neuropathy (less with lenalidomide)
  - More likely to cause weakness and constipation

- **Vincristine:** 30-40% develop neuropathy
  - Sensory and motor neuropathy
  - 1/3 with autonomic neuropathy
Mechanisms Behind Chemotherapy-Induced Neurotoxicity

Platinums, vinca alkaloids, taxanes, thalidomide

Vinca alkaloids, taxanes, bortezomib

Taxanes, Vinca alkaloids, bortezomib, Platinums

Thalidomide, Platinums, Vinca alkaloids

Vinca alkaloids, taxanes, thalidomide
Causes of Neuropathy During Transplant

- Usually related to immune-mediated neuropathies
  - The immune system reconstituting itself after transplant (immune dysregulation)
- Rare (0.36 – 1.04%)
  - Graft vs host disease is a risk factor as is CMV viral infection and unrelated donors
- Can affect the plexus (network of nerves), a spinal nerve root, a single nerve or multiple nerves.
- Treatment:
  - immune suppressants (steroids)
  - immune modulators (IVIG and plasma exchange)
Causes of Neuropathy After Transplant

• Chronic graft vs host disease
  • <1% immune neuropathies
  • 16+ % muscle cramps

• Immune suppressant related:
  • Tacrolimus & cyclosporine- Optic neuropathy
  • TNF alpha (etanercept, infliximab, adalimumab)- immune neuropathies or cranial neuropathies
  • Prednisone- muscle weakness
Diagnosis (Basic)

• Neurologic exam:
  • Check pinprick, fine touch, vibration and position sensation as well as reflexes, strength and balance

• Nerve conduction study/EMG
  • Electrical study measuring nerve function
  • Can be normal early on in course
Diagnosis continued

• Skin biopsy:
  - Small section of skin from three placed on the leg
  - Measure density of the small nerve fibers in the skin

• Laboratory evaluation:
  - Rule out factors which increase risk of neuropathy:
    - Diabetes, vitamin B12 deficiency, high cholesterol, alcohol

*IF a neuropathy progresses AFTER chemotherapy is stopped, look for common risk factors
Diagnosing Autonomic Neuropathy

• Usually based on typical clinical history:
  • Lightheadedness with standing (orthostatic hypotension)
  • Gastrointestinal: early satiety, bloating, constipation or diarrhea,
  • Urinary/sexual: urinary frequency or incontinence, erectile dysfunction

• Autonomic lab testing
  • Checks blood pressure and heart rate during a tilt table test
  • Measures heart rate variability & quantifies
Therapy Options: The Two Tenets

• Targeting/preventing the underlying disease course
  • Treating the underlying cancer: multiple myeloma/amyloidosis
  • Switching or decreasing chemotherapy
  • Treating the risk factors: diabetes, obesity, high cholesterol or low vitamin B12
  • Exercise! (more in a second)

• Targeting symptoms –especially painful features
  • Topical vs oral vs complementary treatments
Exercise - What’s the Evidence?

• Well established in diabetic/pre-diabetic patients:

  After 12 months, nerve fiber density repeated

  Initial nerve fiber density in all patients

  Counseling (40)

  Exercise (60)

• In chemotherapy-induced neuropathy, 2 rodent studies show similar results

Singleton, 2014; Kleckner 2021, Park 2015
Exercise: Why Do It

• A recent systematic review found 16 controlled trials studying exercise, concluding:
  • Exercise can improve quality of life
  • Exercise can improve physical function (balance and strength)
  • Exercise can improve neuropathic pain
  • There are no major risks/side effects with exercise

Guo, 2023
Exercise Prescription

• Regular moderate aerobic fitness: **30 minutes 5 times a week**
  - Biking, walking, swimming, rowing, stairstepper etc
• Exercise to the point where you can’t sing a song
• Overtime, you’ll be able to push it a little more
  - As your fitness level increases, you can go further in the same amount of time
• Adding strength training and balance exercise = icing on the cake
Treatment: The American Society of Clinical Oncology (ASCO) Practice Guidelines (2020)

• **Duloxetine** to help with painful symptoms

• Outside the context of a clinical trial, no recommendations made on:
  • Acupuncture
  • Cryotherapy (frozen gloves and socks)
  • Compression therapy (tight glove)
  • Ganglioside-monosialic acid (fatty acid)
Treatment: ASCO practice guidelines (2020) cont’d

• Clinicians should NOT offer the following for prevention:
  • All-trans retinoic acid
  • Calcium
  • Magnesium
  • L-carnosine
  • Glutamate
  • glutathione
  • Goshajinkigan
  • N-acetylcysteine
  • Omega-3 fatty acids
  • Vitamin B
  • Vitamin E

Loprinzi, 2020
Topical Treatment

• Over the counter:
  • Lidocaine 4-5% ointment/lidocaine patch
  • Salonpas
  • Aspercream
  • Biofreeze
  • Capsaicin - active ingredient of chili
  • CBD ointment/tincture: legality varies by state (if it has THC)

• Prescription: compounded ointment
  • P4 cream:
    • Ketamine
    • Gabapentin
    • Amitriptyline
    • Baclofen
    • Clonidine
    • Nifedipine
    • Tetracaine
Prescription treatments – Equal Efficacy!

• Gabapentin (Neurontin)
  • Low cost; side effects of mild sedation, possible swelling

• Amitriptyline (Elavil)
  • Low cost & helps insomnia/depression; side effect: dry mouth & constipation

• Pregabalin (Lyrica) = next generation of gabapentin
  • Less sedation compared to gabapentin but 10x more expensive

• Duloxetine (Cymbalta) Best studied in chemotherapy induced neuropathy
  • Can help with chronic pain and depression, but more expensive
Non-Pharmacological Options

Complementary Medicine

Supplements

Meditation

Massage

Acupuncture

Physical Therapy

Electrotherapy

Brani 2016, Zhang 2023
Treatment of Autonomic Neuropathy
Orthostatic Hypotension

- Compression stockings (At least 15-20mmHg)
- Abdominal binders
- Optimizing hydration (2-3 Liters/day) –if OK from a cardiac standpoint
- Optimizing salt intake (3+ grams per day) –if OK from a cardiac standpoint
- Raise head of bed by 10-20 degrees
- Medications: midodrine or florinef
Treatment of Autonomic Neuropathy
Gastroparesis, Incontinence, Erectile Dysfunction

• Gastroparesis: delayed emptying due to loss of normal gut motility
  • Dietary modifications: small particle, low fat, regular meals, +/-liquid nutrition and increase hydration
  • Pro-kinetic meds (Reglan 15 min before a meal)

• Urinary Frequency/Urgency/Incontinence
  • Medications: terazosin, oxybutynin etc

• Erectile dysfunction
  • Medications: Viagra, Cialis etc.
Treatment of Mononeuropathies

- Carpal tunnel syndrome
  - Neutral wrist splint (nightly x 6 weeks)
  - Steroid injections or carpal tunnel release

- Cubital tunnel (ulnar neuropathy)
  - Elbow brace (nightly x 6 weeks)
  - Ulnar release at the elbow
Who you gonna call?

• Talk to your hematologist/oncologist first
  • Many feel comfortable prescribing medications for nerve pain
• A neurologist can help confirm and manage neuropathy IF needed
  • If there is diagnostic uncertainty
  • Symptoms are severe
  • Neuropathic pain is not under control with 1st line agents
• *This generally would just require a referral from your primary provider
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Questions?

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