Peripheral Neuropathy in Waldenstrom's Macroglobulinemia

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Peripheral Neuropathy

- a disease or degenerative state of the peripheral nerves in which motor, sensory, or vasomotor nerve fibers may be affected and which is marked by muscle weakness and atrophy, pain, and/or numbness

Common Causes of PN

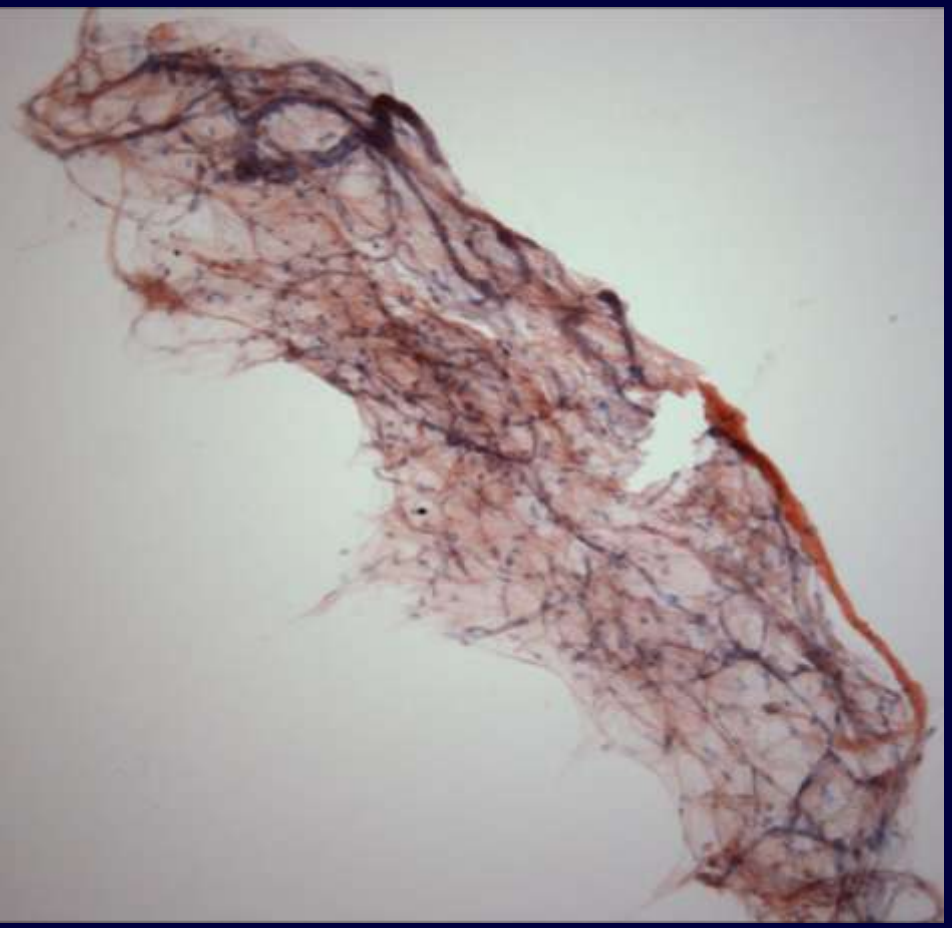
- Chronic disease state:
  - Diabetes
  - Infection (Lyme, HIV)
  - Peripheral Vascular Disease
  - Chronic Liver Disease
  - Cancer
- Vitamin Deficiency
- Overuse Injury
- Alcohol Abuse
- Toxic Exposure
- Rheumatic and/or Genetic Disease

Causes of Peripheral Neuropathy in WM

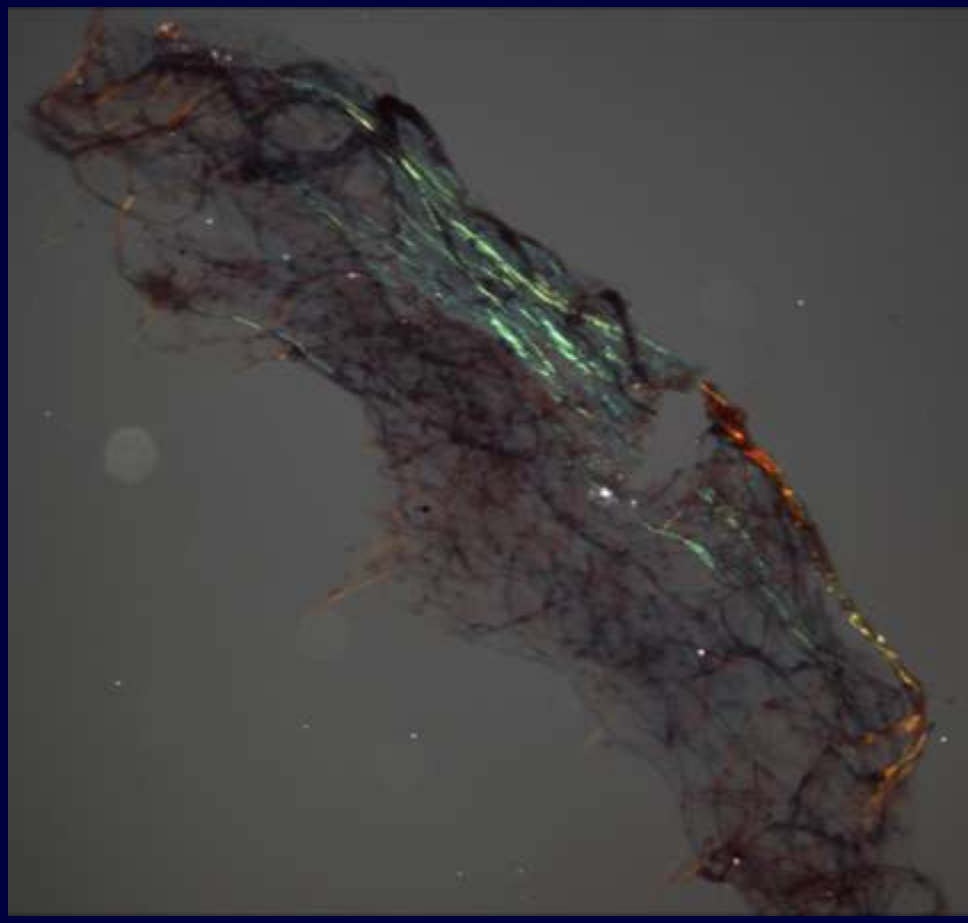
- IgM-related Neuropathic Antibodies
  - Anti-Mag
  - Anti-GM1
  - Anti-Sulfatide
  - Undetermined
- Lymphoplasmacytic Lymphoma cell invasion
- Amyloid
  - a complex protein resembling starch, deposited in tissues in some degenerative diseases

Amyloid

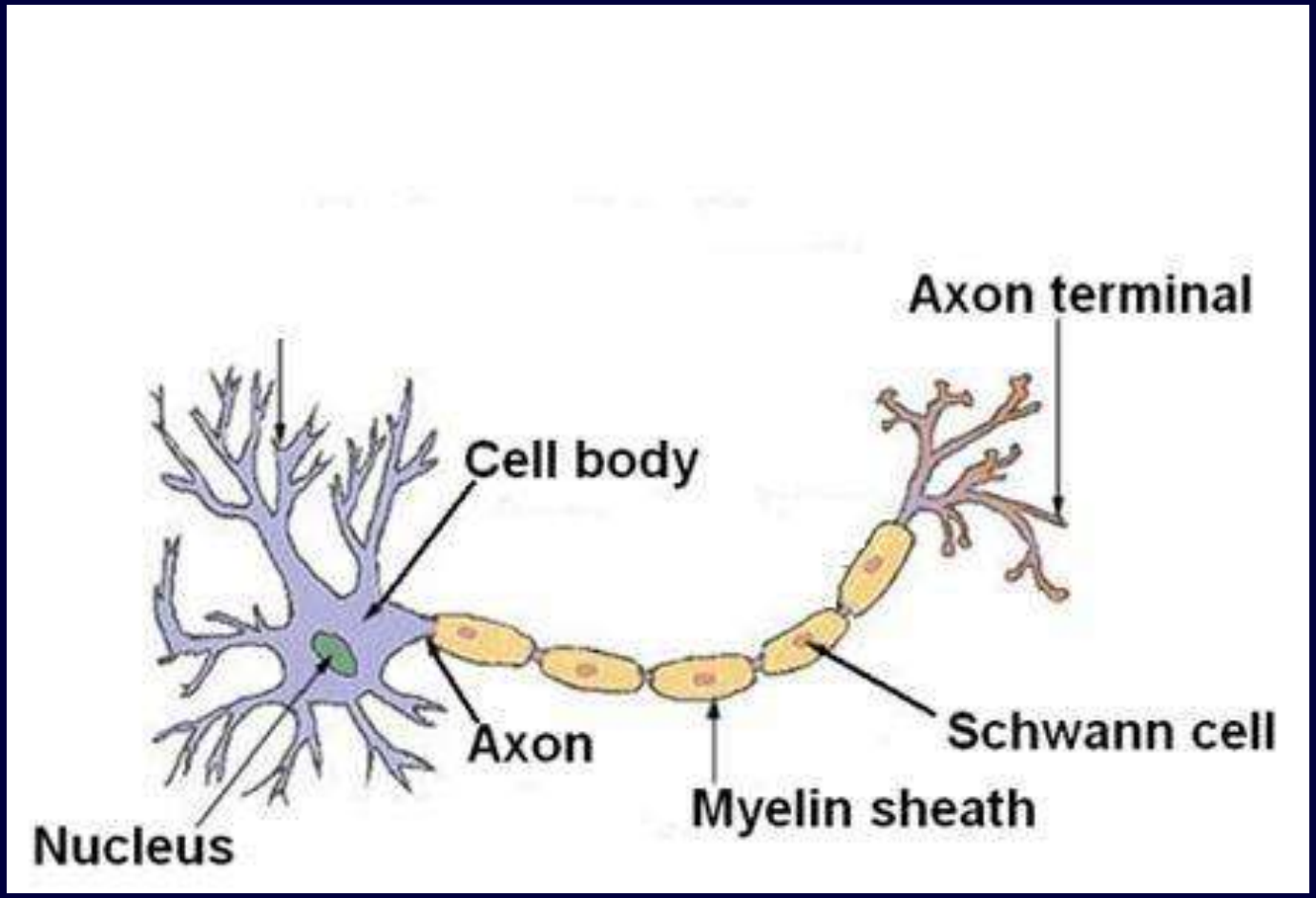
10x Congo Red



10x Congo Red – Polarized



Anatomy of a Nerve Cell



Characteristics of Peripheral Neuropathy in WM

- Chronic
- Progressive
- Symmetric
- Predominantly distal
- Involve sensory nerves
  - Sensation loss, tingling, heat/cold, pain, gait disturbances
- Less commonly involve motor nerves

Paraneoplastic Related Neuropathies in MGUS.

- Unselected cases of Monoclonal Gammopathies
  - IgG (6%)
  - IgA (14%)
  - IgM (31%)
- IgG and IgA related PN often associated with axonal degeneration and motor impairment.
- IgM related PN associated with sensory PN. 30% associated with Myelin Associated Glycoprotein (MAG).

Nobile-Orazio et al. Acta Neurol Scand. 1992 Jun;85(6):383-90.

Long Term Follow-up of Patients with MAG related IgM Neuropathy.

- Number of patients in study = 25
- Mean follow-up of 8.5 yrs.
- Mean duration of neuropathy was 11.8 yrs.
- 17 (68%) alive ; 3/25 died from treatment complication. No pt died from neuropathy.
- 11 (46%) became disabled from their PN.

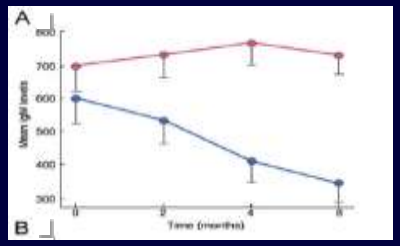
Nobile-Orazio et al. Brain. 2000;123 :710-7.

Randomized Phase II Study of Rituximab in MAG+ IgM PN.

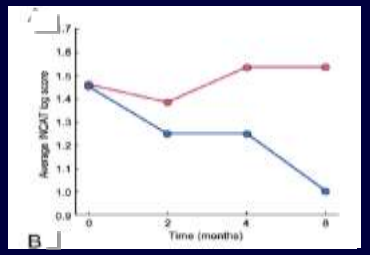
R → Placebo

R → Rituximab 375 mg/m2/wk x 4 wks

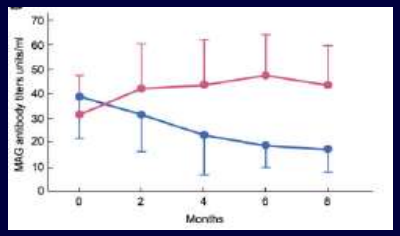
sIgM



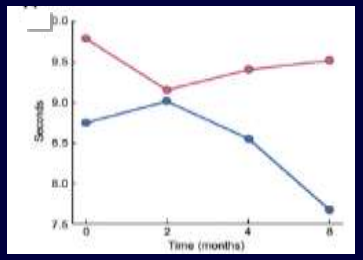
INCAT



MAG



10m walk



Dalakas, Ann Neurol. 2009;65(3):286-93.

Bing Center Study of Patients with PN

- 900 consecutive WM Pts; Pts with treatment and non-disease related PN excluded.
- 199 (22.1%) had diagnosis of disease related PN.

122 had NP Ab testing

24.5% MAG+

1.6% GM1+

0.8% Sulfatide+

61 had Fat Pad or Bone Marrow Congo Red Stain

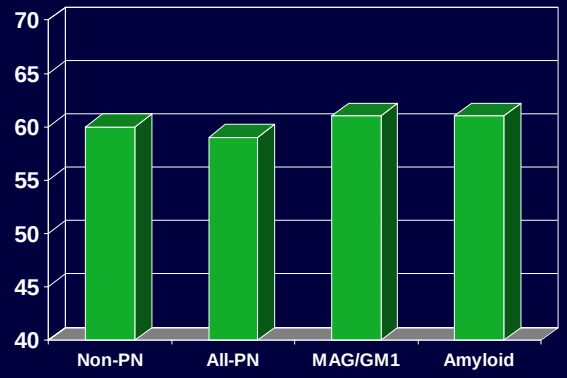
21.3% positive

Only 1 pt also MAG+

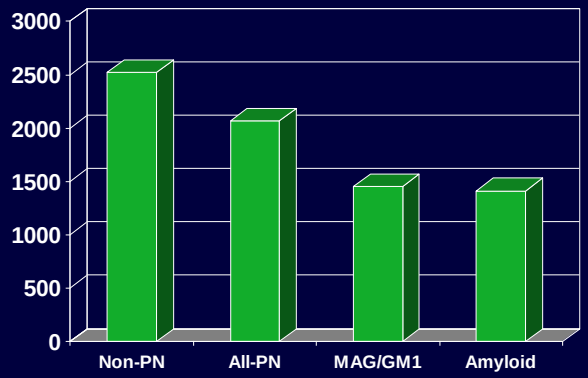
Treon et al, 12th International Symposium on Amyloid, 2010.

Clinical characteristics

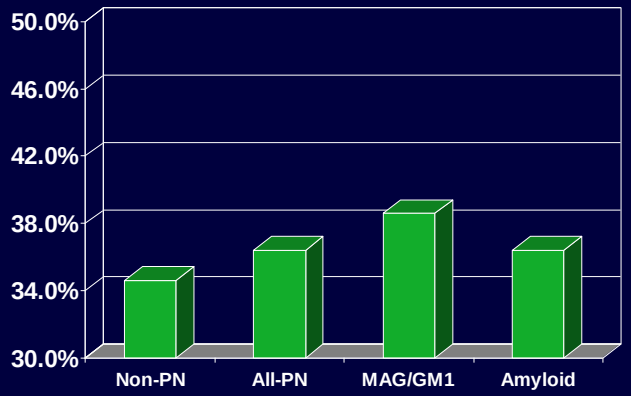
Age



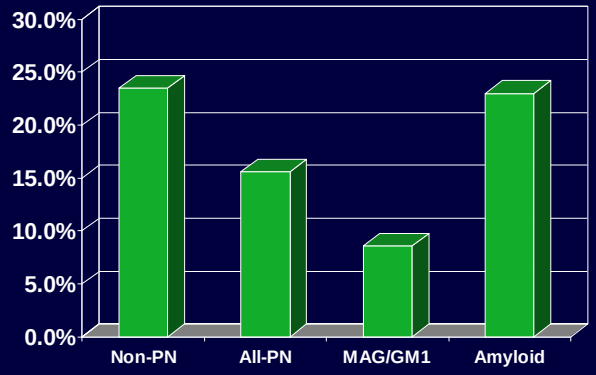
sIgM



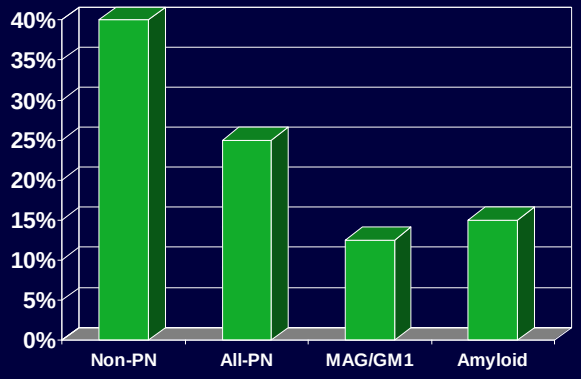
Hct %



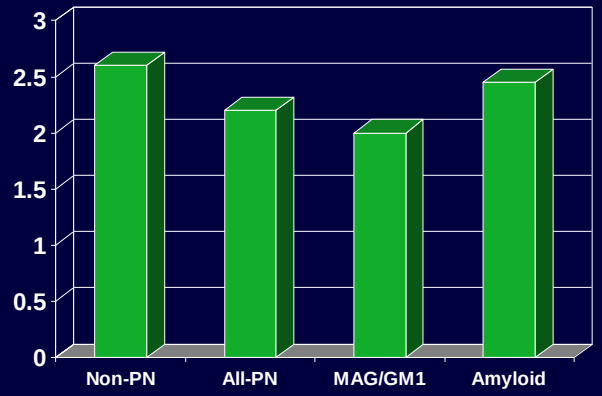
Familial



BM %



B_2M



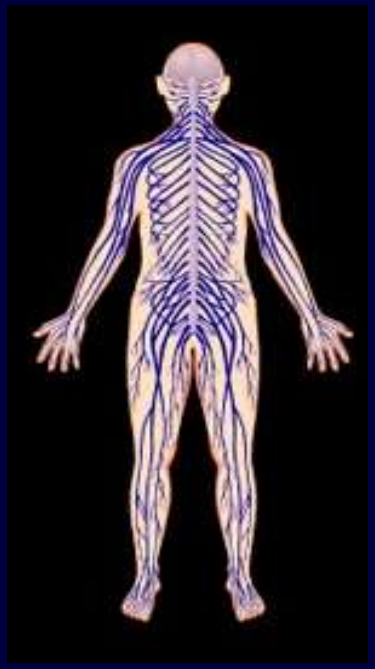
Treon et al, 12th International Symposium on Amyloid, 2010.

Treatment Options for IgM-Related Neuropathy

- **Plasmapheresis**
- **IVIG**
- **Chemotherapy**
  - **Single-agent or combination**

  Rituximab, Cyclophosphamide, IMIDs,

  Nucleoside analogues



Treatment Outcome

- Plasmapheresis

  29/42 (69%) had symptomatic improvement;
- IVIG

  1/8 (12.5%) had symptomatic improvement;
- Chemotherapy

  71/151 (47%) had symptomatic improvement;

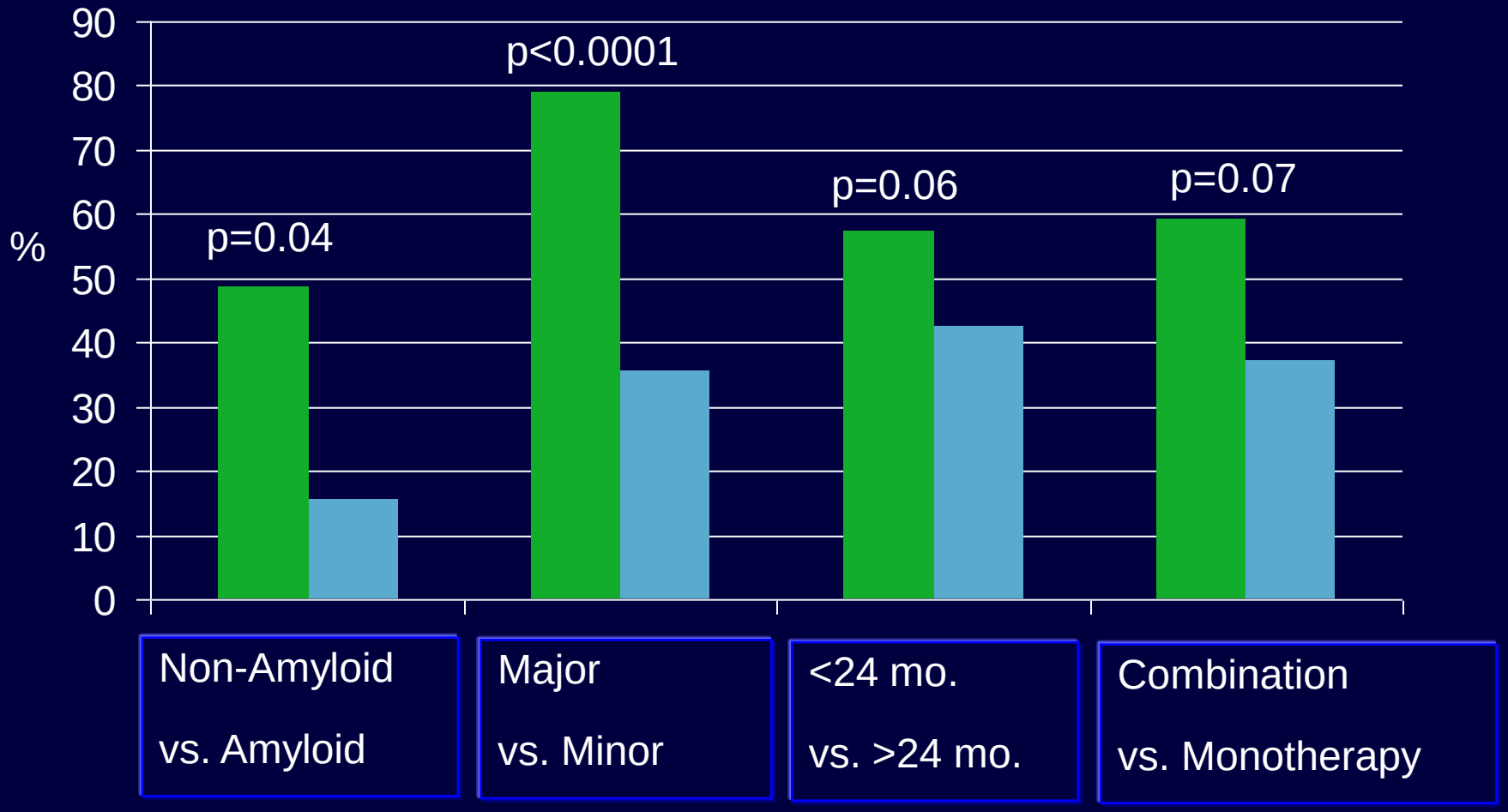
  →8/151 (5.3%) had complete resolution of PN.

Treatment Outcome of WM related PN.

Treatment	N=	Overall RR	Major RR	Improved PN
Oral alkylator	21	33.3%	19.0%	19.0%
Nucleoside analogue	11	45.5%	36.4%	45.5%
Rituximab	57	59.6%	35.1%	42.1%
Rituximab/nucleoside analogue	26	50.0%	46.0%	54.0%
Rituximab/cyclophosphamide	18	83.3%	50.0%	55.6%
Rituximab/thalidomide	7	71.4%	71.4%	71.4%
Rituximab/bortezomib	8	75%	50.0%	75.0%

Treon et al, 12th International Symposium on Amyloid, 2010.

Symptomatic Improvement following Therapy: Subset Analysis



Treon et al, 12th International Symposium on Amyloid, 2010.

Medical Management of PN - MISC

- Acupuncture
- Topical Capsaicin (works by depleting or interfering with substance P, a chemical involved in transmitting pain impulses to the brain. The properties of capsaicin make it an option for relieving pain.)
- Cocoa Butter (rich in Vitamin E, serotonin and xanthines) Apply to affected area twice a day with gentle massage.
- Menthol or Peppermint-based lotions applied gently may also help.

Dietary Supplements for Neuropathy

- ***ALWAYS CHECK WITH YOUR LOCAL PHYSICIAN BEFORE ADDING ANY SUPPLEMENTS***
- ALPHA-LIPOIC ACID
- Gamma linolenac acid
- High-dose B-Complex Multivitamin
- Vitamin E, Vitamin D
- AMINO ACIDS – (NOTE: Can interfere with Velcade).
- ACETYL L- CARNITINE
- FISH OILS - OMEGA

Dietary Supplements for PN - Cramping

- MAGNESIUM
  - 250mg twice a day
- POTASSIUM
  - Bananas, Oranges, Apple cider vinegar
- CALCIUM
  - TUMS, milk, cheese, ice cream
- TONIC WATER (has Quinine in it)
  - Drink one glass in evening and any other time cramping occurs

Medical Management of PN

- **MEDICATIONS** – Prescription needed
- NEURONTIN (gabapentin)
  - Start with 100mg three times a day. Gradually work up to 600mg three times a day.Can dose as high as 2700mg total dose with Physician permission.
- ELAVIL (Amitriptyline) 25-50mg at bedtime
- SINEQUAN (Doxepin) 10-25mg at bedtime
- CYMBALTA (Duloxetine) Start at 20mg, work up to 60mg at bedtime
- LYRICA (Pregabalin) 75-150mg twice a day.
- LIDODERM PATCH 5% Applied topically

Monitoring Peripheral Neuropathy

- Report symptoms to your health care provider
  - What does it feel like?
  - When is it better/worse?
  - Where is it located?
- Expect a detailed Clinical exam:
  - Motor tests (gait, strength, dexterity)
  - Sensory tests (pinprick, vibration, cold)
  - Reflexes
- EMG studies
- Biopsy: Sural Nerve, Punch Biopsy

Challenges

- Goals of therapy: Symptomatic Improvement vs stabilization, CR, prevent further decline?
- Timing of Therapy: Earlier vs. late intervention?
- Optimal Therapy:
  - Integrative therapy options: Acupuncture, supplements
  - Prescription vs. Over-the-counter
  - Mono vs. Combination Therapy?
- Different approach for amyloid vs. non-amyloid patients
- Amyloid diagnostics: consider mass spectometry
- Role of Novel Agents with "Neuropathy Risk"
- Role for Maintenance therapy

Potential Study Areas

- Targeted clinical trials
- Monotherapy vs. Combination Therapy

  i.e. rituximab vs. CDR (IgM related PN)
- Maintenance therapy
- Use of predictive genomics
- Novel agents

  IMiDs (Pomalidomide); Proteasome Inhibitors (MLN4924, 9708, Carfilzomib); mAbs (GA101, Ofatumumab), Bendamustine.
- Symptomatic care (Ampyra/dalfampridine).

The Bing Center Team

THANK *YOU!*

Thank you to the 900 patients who agreed to participate in our research. Allowing our team to review your information directly resulted in new information which is guiding our treatments and future studies.