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On Waldenström's macroglobulinemia and IgM related disorders

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Chapter 4

Investigation and management of peripheral neuropathies associated with Waldenströms macroglobulinaemia and IgM monoclonal gammopathies: recommendations from the IWWM-8 consensus panel

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ABSTRACT

The International Workshops on Waldenström's macroglobulinaemia (WM) have proposed criteria for clinicopathological diagnosis and initiation of therapy in WM patients¹, assessment of treatment response², and treatment recommendations, that were last updated in 2014³. As part of its latest consensus deliberations (IWWM8, London, UK, August 2014), the panel considered the approach to the diagnosis and management of peripheral neuropathies (PN) associated with IgM monoclonal gammopathies, including WM.

Paraproteinaemic neuropathies are a heterogeneous group of disorders that are difficult to classify, due to differences in clinical and electrophysiological features as well as the diversity of the haematological dyscrasias with which they are associated. Their prevalence is not precisely known but they are thought to be frequently associated with MGUS and WM. Their consequences are significant and challenging for those affected and for the physicians looking after them. Patients present through different clinical settings including general medical, haematological or neurological specialties and consequently, the clinical work up varies; currently there is no consensus about what should constitute a baseline assessment.

Monoclonal gammopathy of undetermined significance can be of any heavy chain class and in large series approximately 60% were IgG, 10-27% IgM and the remainder IgA^{4,5}. When associated with a neuropathy, the IgM class of paraproteins is heavily over-represented with about 55% of patients having IgM, 35% having IgG and 10% having IgA paraproteins. The prevalence of peripheral neuropathy in persons with monoclonal gammopathy of uncertain significance (MGUS) is approximately 5% in IgG, 15% in IgA and 30-50% in IgM MGUS⁶⁻⁹. However, the prevalence rates of MGUS and peripheral neuropathy are variable and depend on patient selection bias and the vigour with which the presence of an M protein and peripheral neuropathy are sought¹⁰. Monoclonal gammopathies are common with a prevalence of 1% of the general population aged 50 and increasing to 8-9% by the age of 90¹¹. Peripheral neuropathy also affects 2.4% of the general population, increasing to 8.0% with advancing age¹². A frequent challenge therefore is to decide causality of the MGUS versus coincidental association.

Triggers for initiating therapy also lack consensus; the presence of a neuropathy alone should not be a justification for treatment, but progression over weeks or months, accumulating disability and early stage disease should prompt consideration of treatment. The choice of the most appropriate interventions is also difficult because there is inadequate evidence to recommend specific therapies¹³. The outcomes of clinical trials in this area have been hampered by the rarity of definite causally related cases for trial inclusion, their heterogeneity and a reliance on ordinal multi-item composite outcome measures that lack simplicity, reliability, statistical validity and responsiveness^{14, 15}. At

present there are no definite biomarkers to indicate which patients would benefit from treatment or to follow the effects of therapy.

This paper will focus on IgM-related neuropathies; non-IgM entities will be mentioned for clinical comparison. The purpose of this consensus document is to provide a uniform approach to investigating, treating and following up patients with IgM-associated PPN, as well as to suggest appropriate methods for assessing outcomes following intervention.

1. DIAGNOSTIC EVALUATION

1.1 General Work up

Evaluation of a PN in the presence of a paraprotein requires parallel investigation of each entity. The purpose is to establish the nature of the monoclonal gammopathy as MGUS, asymptomatic or symptomatic lymphoproliferative disease (LPD) (**Table 1**). A clinical history and examination are able to delineate most of the initial important features of the clinical phenotype of the PN and are the key to further appropriate testing and management. (**Table 2**). Assessment of the PN requires historical consideration of the nature of the symptoms, the speed of onset, the clinical course and the rate of change, their effect on functional abilities (disability), and associated features. The features of the neuropathy on examination can be enlightening and generally POEMS and anti-MAG neuropathies are easily distinguished from other causes.

Table 1. Work up for monoclonal gammopathy

History	Examination	Investigations
Assessment of wellbeing and performance status	Lymphadenopathy	Full blood count
Fatigue	Hepatosplenomegaly	Renal function
Weight loss	Macroglossia	Liver function
Fevers	Postural hypotension	Bone chemistry
Infections		NT-proBNP
Symptoms of hyperviscosity		HIV serology
		Hepatitis B and C serology
Clinical manifestations of cryoglobulinemia such as purpura,digital ischaemia, arthralgia, fever, Raynaud phenomenon		Lactate dehydrogenase
		b2microglobulin
		Cryoglobulin testing
		Serum free light chains
		SPEP, Immunofixation
		Urinalysis including UPEP
Clinical manifestations of AL amyloidosis, such as unexplained cardiac failure, gut dysmotility, purpura		Bone marrow cytology, biopsy (with Congo red stain if suspicion of amyloid) and MYD88 L265P detection
		CT chest, abdomen, pelvis

CT, computed tomography; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro b-type natriuretic peptide; SPEP, serum protein electrophoresis, UPEP, urine protein electrophoresis.

Neurophysiology (see below) is critical to the assessment of a peripheral neuropathy identified on clinical examination and should be considered an extension of the clinical examination itself. Appropriate laboratory and radiological investigations must be carried out to complete the investigation. (See **Table 2** and below). A number of blood investigations are performed in specific circumstances. Anti-MAG and most relevant anti-ganglioside antibodies in other chronic neuropathies are IgM only (thus there is no point in requesting these unless the paraprotein is IgM). Endocrine tests and vascular endothelial growth factor (VEGF) are critical to the diagnosis of POEMS. Assessment for cryoglobulins and markers of lung and renal function are important if vasculitis is suspected. If AL amyloidosis is suspected (see section 3.5), serum NT-pro-BNP should be measured since it is the most sensitive and early marker of amyloid cardiac involvement. This is clinically relevant since amyloid cardiomyopathy determines the survival.¹⁶ Familial Amyloid Polyneuropathy (FAP) can coexist with a paraprotein and transthyretin (TTR) genetic sequencing is both straightforward and indicated.

The conclusions from these investigations, based on a discussion between a haematologist and neurologist should provide a foundation to establish whether the PN is related to the monoclonal gammopathy and whether there is a need for treatment.

Table 2 Work up of the peripheral neuropathy.

History	Examination	Investigations
Duration of symptoms	Full examination of	Serum B12 and folate
Clinical course (relapsing/remitting/monophasic)	peripheral and central nervous system	HbA1C
Rate of progression	Wasting	Enzyme immunoassay or Indirect immunofluorescence assay for suspected Lyme disease
	Fasciculation	
Sensory/motor predominance		Nerve conduction studies/ electromyography
Topographic distribution (symmetry/ distal/ proximal/ multifocal/cranial nerve involvement)		Anti-MAG antibodies Anti-ganglioside antibodies (GQ1b, GM1, GD1a, GD1b, SGPG)
Falls		VEGF if POEMS is suspected
Postural dizziness		CSF examination for cells including cytology, immunophenotyping and molecular studies
Ataxia		CSF examination for protein including immunofixation Appropriate neuroimaging to rule out infiltration if suspected Nerve biopsy if indicated

CSF, cerebrospinal fluid; MAG, myelin associated glycoprotein; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes; VEGF, vascular endothelial growth factor.

An important consideration in the work up of a possible paraproteinaemic neuropathy is whether electrophysiological tests, cerebrospinal fluid (CSF) examination or a nerve biopsy are indicated (see below). Such investigations may be helpful in selected cases but should be avoided if they are unlikely to change the outcome, to avoid the risk of procedural complications. In some instances, dedicated magnetic resonance (MR) imaging can be useful and is non-invasive; specialised sequences with and without gadolinium may identify nerve root or trunk abnormalities or identify leptomeningeal involvement when relevant symptoms or signs are present. MRI is best carried out in centres with the expertise to perform these specific sequences and interpret them.

Recommendations:

- *Clinical history and examination, by both a haematologist and a neurologist, to delineate the key features of the monoclonal gammopathy and neuropathy and to guide if further investigation should be performed in all cases.*
- *Neurophysiology is mandatory where a neuropathy is identified on clinical examination (see below).*
- *Appropriate laboratory and radiology investigations should be performed.*
- *If AL amyloidosis is a possibility, appropriate cardiac biomarkers and tissue biopsy should be performed (see below).*
- *If AL amyloid, vasculitis or infiltration are suspected and other relevant investigations are inconclusive, nerve biopsy maybe considered, which should be performed in a centre with appropriate expertise*
- *CSF examination should be considered in demyelinating neuropathies.*
- *MRI neurography can be helpful to guide further investigation or biopsy in rare cases.*

1.2 Nerve conduction tests and electromyography

Nerve conduction studies (NCS) and electromyography (EMG) characterise the nature, pattern and extent of nerve damage. Where the neurophysiologist and the referring clinician are not the same person it is useful to have a specific question or questions that need to be answered when requesting NCS. In difficult cases, it is helpful to discuss the referral with the neurophysiologist. In straightforward conditions an initial standard protocol is followed, but the investigator may modify or add to these tests on the basis of the initial findings.

There are few contraindications to NCS. The implantation of some cardiac pacemakers may contraindicate NCS. Discussion with the patient's cardiologist is advised if the NCS are likely to involve stimulation close to the chest wall, as life threatening events can be triggered by an external voltage applied in close proximity to an implantable cardioverter/defibrillator device. Anticoagulants are associated with a risk of intramuscular

haematoma with EMG needling. Where EMG is necessary anticoagulants might need to be suspended prior to an examination.

Peripheral nerves contain fibres of different diameters and degrees of myelination and hence the conduction velocities vary. Recorded potentials are compound responses. Motor responses are transduced through muscle (compound muscle action potential or CMAP) and a massed action potential is recorded from sensory nerves (sensory nerve action potential or SNAP). Multiple characteristics of the NCS are considered including size and shape of the CMAP, the conduction velocity, the velocity gradient, conduction block or dispersion and abnormalities of the F-wave, a useful indicator of proximal peripheral nerve pathology. The terminal latency index (TLi) gives an indication of preferential distal slowing and with a TLi in more than one nerve of <0.25 , anti-MAG neuropathy has an increased likelihood¹⁷. Features indicative of axonal and demyelinating neuropathy are shown in **Table 3**.

Table 3: Typical nerve conduction study abnormalities seen with axonal loss or demyelination.

	Axonal loss	Demyelination
Sensory responses	Small or absent	Small or absent
Distal motor latency	Normal or slightly prolonged	Prolonged
CMAP amplitude	Small	Normal (reduced if conduction block or temporal dispersion)
Conduction block/temporal dispersion	Not present (responses may disperse slightly)	Present
Motor conduction velocity	Normal or slightly reduced	Notably reduced
F waves minimum latency	Normal or slightly prolonged	Significantly prolonged

CMAP, compound muscle action potential.

Recommendations:

Neurophysiological studies should be carried out to confirm the characteristics of an identified neuropathy to guide diagnosis and further investigation and treatment.

1.3 CSF Examination

CSF protein is elevated in 75-86% of demyelinating paraproteinaemic neuropathy¹⁸. In cases where there is an atypical phenotype or mixed demyelinating/axonal electrophysiology, the finding of a raised CSF protein of $>1.0\text{g/l}$ (normal usually $<0.45\text{ g/l}$) can be supportive of an immune-mediated pathology (NB raised CSF protein can also occur in many other conditions such as diabetes and hereditary neuropathies). If infiltration of the peripheral nerves or CNS is suspected, the presence of malignant cells can be sought with immunocytology and/or flow cytometry to avoid missing the diagnosis of this critical pathology. A single large volume (10ml) CSF sample for cytology will have

about a 50% chance of identifying pathological cells when present; three 10ml samples increases the pick-up rate to about 90%. Using a highly sensitive real time quantitative PCR (qPCR) technique, MYD88 L265P can be detected in the CSF¹⁹, so this technique could be considered to corroborate the findings. Since the qPCR is a very sensitive technique, caution must be taken to avoid blood contamination of the CSF since MYD88 L265P can also be detected in peripheral blood²⁰.

Recommendations:

- *In cases of demyelinating neuropathy, although not mandatory, examination of the CSF supports the diagnosis if the protein is raised and other biochemical constituents are normal.*
- *When the clinical work up is unrevealing or inconclusive, and a malignant meningitis or invasion of the CNS is suspected, examination of the CSF is indicated up to three times for cellular constituents. If cellular material is identified, then cytological examination and/or immunophenotyping is required to characterise the population.*

1.4 Nerve Biopsy

The indications for nerve biopsy are increasingly limited. Sensory nerve biopsies are invasive and associated with a permanent sensory deficit and a 10% risk of post biopsy pain. A sensory nerve biopsy is recommended when the neuropathy is likely to be secondary to amyloid, vasculitis or direct invasion or is progressive and threatens to become debilitating and a comprehensive systemic work up has failed to identify a cause. If amyloidosis is suspected, alternative sites for diagnosis should be explored first, such as an abdominal fat aspirate for amyloid plus bone marrow biopsy (positive in >90% of patients with AL amyloidosis,²¹) or genetic testing for transthyretin (TTR) mutations. Where histological evidence for amyloid has been found in other tissues, and the clinical and neurophysiological characteristics of the PN are compatible with amyloidosis, a nerve biopsy is usually not required.

The superficial peroneal nerve or the sural nerve are usually examined, but only when clinically and electrophysiologically affected (performing a biopsy of an electrically normal nerve is associated with greater rates of post biopsy pain). When only the upper limbs are affected, the superficial radial nerve or a dorsal cutaneous branch of the ulnar nerve can be biopsied, guided by clinical and NCS findings.

It is recommended that nerve biopsy is *only* performed in centres with surgeons experienced in the technique and that the specimen is prepared for and analysed by a laboratory with experience in staining and interpreting nerve pathology.

Light microscopy of formalin-fixed, paraffin-embedded tissue is the most important method for establishing a definitive diagnosis such as vasculitis, amyloidosis or lymphoma. Electron microscopic examination of nerve fibre specimens for the study

of unmyelinated fibres is occasionally required. Frozen sections can be both quickly examined and also used for some immunohistochemical stains. If the initial microscopic examination is not informative and a suspicion of vasculitis or amyloid is strong, further sectioning of the tissue is indicated to search for a definitive lesion. In suspected vasculitis, stains for the internal elastic lamina of arteries and peri-arterial hemosiderin can provide indirect evidence for the diagnosis in the absence of a definitive lesion, such as inflammatory infiltration of the blood vessel wall or fibrinoid necrosis²². Congo red staining using Pearson's method identifies amyloid, which can be further subclassified by immunohistochemistry to identify transthyretin(familial) or immunoglobulin light chain²³; staining of light chains requires sections prepared from unfixed frozen tissue and is technically difficult to perform and interpret. In case of suspected lymphomatous infiltration, an immunohistochemical search for monoclonal B cells is mandatory, although the diagnostic yield is often low due to the small sample size.

Recommendations:

- *Where a comprehensive systemic work up has failed to identify a cause and there remains a suspicion of amyloid, vasculitis or direct cellular invasion, in atypical cases unresponsive to treatment, or progressive conditions which threaten to become debilitating, a sensory nerve biopsy may be indicated.*
- *The risk-benefit ratio of carrying out the biopsy needs to be carefully weighed, in particular whether the procedure is likely to alter the course of management.*
- *The need for a nerve biopsy should be ratified by a neurologist with a specialist interest in PN and carried out by experienced surgeons and examined by experienced laboratories for maximum yield.*

1.5 Skin biopsies

Skin biopsy samples of full thickness skin stained for neuron and neuroendocrine cell specific PGP9.5 (UCHL-1) may be useful for histological confirmation of a small fibre neuropathy. The procedure is performed with a 3mm disposable punch under topical anaesthesia. Biopsies are taken 10 cm above the lateral malleolus, and 20 cm below the iliac spine to demonstrate a generalised or length-dependent process. Skin biopsy may be performed in patients with symptoms of small-fibre neuropathy (see section 3.6) when the nerve conduction studies do not reveal any large fibre abnormalities. Pre-ganglionic sensory neuropathies will have a patchy and dermatomal rather than a distal onset and normal small fibre densities²⁴. Normative values for quantitation are available. Procedural risks are very low, and complications are rare

The quantitation of unmyelinated dermal and epidermal fibres using bright-field immunohistochemistry or indirect immunofluorescence can provide diagnostic information to support clinical and neurophysiological tests. Dermal fibre analysis is developing in

usefulness for demonstrating IgM deposits on myelinated nerve fibres²⁵. Thermal threshold and other quantitative small fibre and autonomic tests (QSART) can support a clinical diagnosis of small fibre neuropathy. These remain specialist tests, and are not routinely available.

Unfortunately, skin biopsies do not provide pathognomic information, limiting their usefulness. The technique cannot at present replace nerve biopsy when neuropathological examination of mixed or large-fibre neuropathy is needed and when a vasculitis or amyloid is suspected and should not be done.

Recommendations:

Skin biopsy maybe performed for histological confirmation of a small fibre neuropathy when the nerve conduction studies do not reveal any large fibre abnormalities but requires specialist analysis and rarely provides information that alters the management of the patient and is therefore not routinely recommended.

1.6 Imaging

Imaging of the neuraxis is indicated in selected cases where there are mixed central and peripheral nervous system features, evidence of central disease (Bing-Neel syndrome), suspected neural compression, leptomeningeal or radicular infiltration²⁶. Features indicative of leptomeningeal involvement include leptomeningeal, subependymal, or dural enhancement; cranial nerve enlargement and enhancement, superficial cerebral lesions and hydrocephalus. Spinal MRI can reveal enhancing intradural soft tissue, thickening and enhancement of nerve roots, and leptomeningeal enhancement²⁷. Neurolymphomatosis is characterised by nodular or diffuse thickening of nerves and contrast enhancement affecting the peripheral nerves, spinal roots, cranial nerves or plexi (brachial or lumbar)²⁸.

The sites to be imaged depend on localising clinical features identified from the clinical and neurophysiological examination. Consideration should be given to the appropriate imaging modality. Specific MR sequences with or without gadolinium enhancement in discussion with an appropriately experienced radiologist can identify abnormal neural tissue in the central and peripheral nervous system. Ultrasound scanning can identify focal and more extensive thickened nerves in the distal limbs. Neither modality has the capacity to diagnose the nature of nervous system lesions, but will add to diagnostic information and may target biopsy in specialised centres.

MRI should be performed prior to a diagnostic lumbar puncture for CSF analysis, as false-positive leptomeningeal enhancement may result from iatrogenic meningeal irritation.

Recommendations:

- Targeted MRI may be helpful in assisting with diagnosis and also in clarifying sites of neural involvement otherwise difficult to assess.
- MRI, CT and Ultrasound may help target diagnostic biopsies in specialist centres.
- Prior discussion with an experienced neuroradiologist will ensure that the correct sequences are performed with appropriate Gadolinium enhancement.
- MRI of the neuraxis should be performed prior to lumbar puncture to avoid false positive meningeal enhancement.

2. CLINICAL PHENOTYPES

In the presence of a neuropathy with known electrophysiological characteristics, the immunoglobulin class can help to focus investigation and suggest if there is a relevant link. The following statements act as a useful guide:

- A causal relationship between the paraprotein and a neuropathy is more likely in the setting of IgM compared to IgG or IgA monoclonal gammopathies¹⁸. In the presence of an IgM MGUS or WM and high titres of anti-MAG antibodies (for example 'strongly positive' or > 70,000 BTU in the Bühlmann ELISA assay), if the nerve biopsy shows IgM or complement deposits on myelin, or electron microscopy shows widely-spaced myelin, a causal relationship between the paraprotein and PN is highly probable.
- An IgM paraprotein with high titres of IgM antibodies to other neural antigens (such as GD1a, GD1b, GM2) and a slowly progressive predominantly distal neuropathy may be causally associated.
- An IgM paraprotein with a high titre of anti-GM1 associated with a multifocal motor neuropathy is likely to be causally linked.
- An IgM paraprotein with a high titre of antibodies against disialylated gangliosides (GQ1b, GT1a, GT1b, GD1b, GD2 and GD3) and a neuropathy with ophthalmoplegia and ataxia (CANOMAD) is likely associated.
- A causal antibody targeted relationship is *less* likely in IgM MGUS anti-MAG negative cases where :
 - o Time to peak of PN <6 months, as this is usually a slowly progressive condition. Guillain-Barré Syndrome reaches a nadir by definition in <4 weeks; CIDP must progress or relapse beyond 8 weeks. Other aggressive neuropathies where the paraprotein deposits as an AL amyloid or drives vasculitis may peak quickly.
 - o Relapsing and remitting or course more suggestive of CIDP
 - o Cranial nerve involvement (except CANOMAD)
 - o Non-symmetrical distribution (consider vasculitis, hereditary neuropathy with liability to pressure palsies (HNPP), diabetes (+/- pressure palsies)

- o History of infection immediately preceding the onset (GBS, polio and other viral neuroinvasive diseases, HIV, diphtheria, Lyme, leprosy).
- IgG and IgA neuropathies associated with neuropathies are more often CIDP with a coincidental paraprotein. Causal associations between IgG and IgA paraproteins and neuropathy are more often related to the light chain as AL amyloid or POEMS and thus in general have a worse prognosis.
- No IgG paraproteins with consistent antigenic targeting activity against neural epitopes causative of disease are yet described.

Investigation of the WM and the PN utilising the methodology outlined in **Tables 1 and 2** can provide enough evidence to formulate a diagnostic categorisation of the neuropathy. A schematic decision tree is shown in **Figure 1**, which assists in clarifying the pathways to particular WM associated diagnoses. In the following section, the most common clinical entities will be addressed.

2.1 IgM MGUS-associated PN

IgM MGUS with a demyelinating PN is the most common category of paraproteinaemic neuropathy. The characteristic clinical phenotype is a predominantly distal, chronic (> 6 months), symmetrical, painless neuropathy with a predominance of sensory symptoms (the so-called Distal, Acquired, Demyelinating, Sensory or DADS phenotype), frequent imbalance sometimes bordering on ataxia, tremor (up to 89% at onset, 15% disabling) and mild or minimal weakness^{29, 30}. This phenotype is most commonly associated with anti-MAG antibodies (see below)³¹. However, there are not infrequent departures from these typical features, with some patients having more prominent ataxia and others demonstrating proximal weakness reminiscent of CIDP³¹.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) can be associated with IgG or IgA paraproteinaemic neuropathy and a causal relationship with the paraprotein is less certain. Patients with CIDP have proximal and distal weakness, motor and sensory impairment and recognisable patchy demyelinating motor and sensory electrophysiological abnormalities. Patients with associated IgG and IgA paraproteins are indistinguishable from chronic inflammatory demyelinating polyneuropathy (CIDP)³² and thus frequently more rapidly progressive than IgM PPN^{33, 34}.

Rapid progression, a mixed axonal and demyelinating or an axonal predominant PN should raise the possibility of primary (AL) amyloidosis, especially if neuropathic pain or autonomic dysfunction are prominent³⁵. Cryoglobulinaemia may be associated with a distal, symmetrical, predominantly sensory neuropathy with painful dysesthesias and sensory loss in a stocking distribution and varying degrees of motor involvement (none to severe weakness) usually involving the lower limbs³⁶. If suspected, it is important to pursue the specific diagnostic tests needed to confirm these conditions, such as tissue biopsy with Congo red staining for amyloidosis or cryoglobulins testing³⁷.

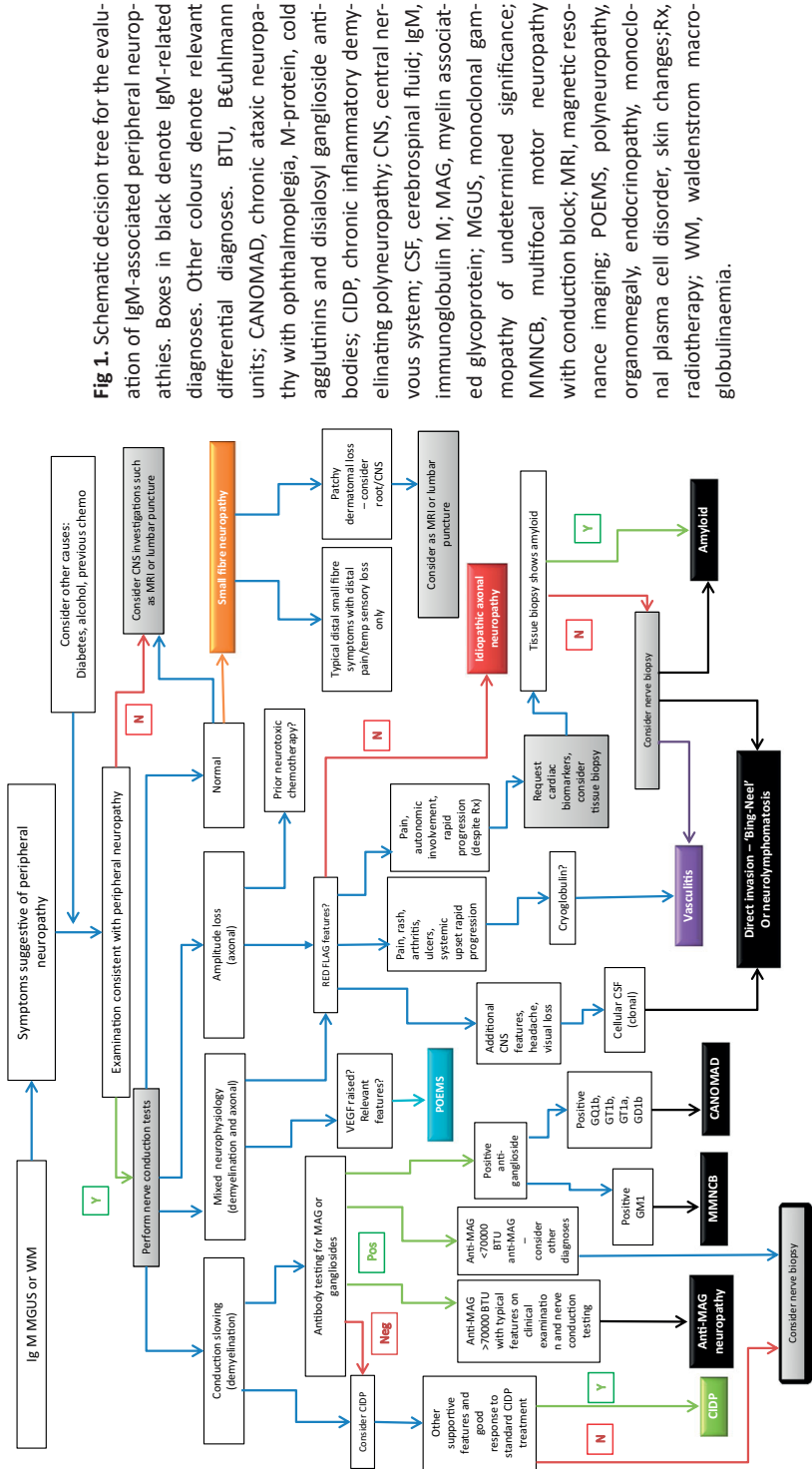


Fig 1. Schematic decision tree for the evaluation of IgM-associated peripheral neuropathies. Boxes in black denote IgM-related diagnoses. Other colours denote relevant differential diagnoses. BTU, B β uhmann units; CANOMAD, chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl ganglioside antibodies; CIPD, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; CSF, cerebrospinal fluid; IgM, immunoglobulin M; MAG, myelin associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; MMNCB, multifocal motor neuropathy with conduction block; MRI, magnetic resonance imaging; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes; Rx, radiotherapy; WM, Waldenström macroglobulinaemia.

2.2 Anti-MAG antibody-associated PN

Up to 50% of patients with IgM-associated demyelinating PN have anti-myelin associated glycoprotein (MAG) antibodies, most commonly IgM κ rather than λ ³⁸. Anti-MAG neuropathies usually occur in the setting of IgM MGUS, but may also be seen in patients with Waldenström's macroglobulinaemia³⁹. The typical age of onset is 60+ years and the course of the disease is insidious; in up to 50% patients, significant disability develops 10-15 years following the diagnosis²⁹.

All patients with IgM-associated demyelinating PN should be tested for anti-MAG antibodies; the Bühlmann anti-MAG ELISA is the most sensitive method. A clinically significant result is strongly positive (> 70000 BTU). Weakly positive (1000- 7000) or positive (7000- 70000 BTU) anti-MAG antibodies are less specific and may occur in the absence of a PN. Low titres of anti-MAG IgM (1:200 or less) have been detected in 17 of 101 control patients without IgM M-proteins⁴⁰. The presence of low levels of anti-MAG IgM in a significant proportion of controls suggests that monoclonal expansion of naturally occurring B-cell clones secreting anti-MAG IgM may be responsible for the high incidence of this antigen specificity of the M-protein.

If the anti-MAG assay is negative in the presence of an IgM-associated PN, testing for IgM antibodies against other neural targets including the gangliosides, GQ1b, GM1, GD1a, GD1b and SGPG should be undertaken which may be supportive of a link between the paraprotein and the PN.

The electrophysiological features associated with anti-MAG IgM demyelinating PN are readily recognisable. Motor conduction velocities are slowed, sensory nerves are prominently involved, often with absence of action potentials and there is disproportionate prolongation of the distal motor latency (DML). Conduction block and abnormal temporal dispersion which are more typically seen in CIDP are very rare in this setting¹⁸. Specific features do not need to be present and electrophysiological test results may resemble CIDP⁴¹.

2.3 Waldenström's-associated PN

Symptoms of PN are present in about 20% of patients with WM at diagnosis, and up to 50% are affected at some time in the course of their disease⁴². Most often the PN resembles that seen in IgM MGUS: distal chronic symmetrical predominantly sensory polyneuropathy. Nerve conduction studies typically show evidence of demyelination with prolonged DML and reduced conduction velocities. As always, there are exceptions, with distal axonal neuropathies seen in some and mixed axonal and demyelinating neuropathies in others, especially when anti-MAG is negative⁴³. When present at a significant titre, anti-MAG antibodies are probably pathogenic in this setting. When atypical clinical or electrophysiological features are present, other pathologies including AL amyloidosis, cryoglobulinaemia, neurolymphomatosis (direct tumoural invasion of peripheral nerves),

vasculitis or IgM binding to hitherto unidentified neural antigens may be instrumental and appropriate investigations should be undertaken.

Where neurotoxic therapy has been used, chemotherapy-induced PN may be present and will need to be distinguished from WM-associated PN, based on the temporal pattern and character.

2.4 CANOMAD

Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl ganglioside (IgM Anti-GD1b/GT1b/GQ1b) antibodies is a rare chronic neuropathy which presents as a chronic painless sensory ataxia and is associated with PN and cranial nerve involvement⁴⁴. Onset is usually in the 5th decade and although the clinical picture resembles that of the Miller-Fisher syndrome, there is a longer course which may have relapsing and remitting symptoms. NCS show a mixed picture of axonal and demyelinating features including very low or absent sensory action potentials and degrees of slow motor conduction velocities.

2.5 AL Amyloidosis

AL amyloidosis should always be considered as a contributor or principal cause in the pathogenesis of the PPN. Other features of amyloidosis must be actively sought, such as cardiac insufficiency and arrhythmia, renal involvement with proteinuria and increased creatinine, autonomic neuropathy (gut dysmotility, erectile dysfunction, gustatory sweating and orthostatic hypotension), GI bleeding, macroglossia and bleeding diathesis. Early recognition is more likely to curtail irreversible organ damage and reduce mortality. To this end screening for AL amyloidosis in those who may have the diagnosis can be performed using two simple and powerful biomarkers, serum NT-proBNP and urinary albumin, that can detect early amyloidosis in 97% of patients.⁴⁵

PN is reported as a symptomatic clinical feature in up to 20% of patients with AL amyloidosis, and evidence for a subclinical PN is found in 35% of patients^{46, 47}. Common presentations include a progressive, painful small fibre predominant length-dependent PN which typically starts in the feet, accompanied by an autonomic neuropathy in about 65% of cases⁴⁷. Amyloid can cause nerve damage by other mechanisms; entrapment neuropathies including carpal tunnel syndrome from compressive infiltration of the flexor retinaculum, and neural or radicular infiltration by amyloid resulting in multifocal mononeuropathies, lumbosacral or brachial radiculopathies and cranial neuropathies in the absence of a polyneuropathy^{46, 47}. When amyloid is proven, if atypical features are present, familial forms of amyloid should be excluded using DNA analysis of the transthyretin gene.

Progression is typically relentless with eventual involvement of large sensory and motor fibres. Nerve conduction studies show a symmetrical, axonal sensorimotor

neuropathy but a definitive diagnosis requires the demonstration of amyloid in a tissue. The most accessible and innocuous biopsy site is the periumbilical abdominal fat that shows Congo red positive deposits in 80% of patients⁴⁸. When combined with Congo red analysis of bone marrow, the sensitivity reaches 90% or more. In the rare patients in whom both biopsies are negative, a nerve biopsy might be considered. Amyloid deposits are found by Congo red staining in the epineurial and endoneurial connective tissue and expanding blood vessel walls. The sensitivity of nerve biopsy for detecting amyloid varies from 30-100%⁴⁹, depending upon the size and site of the biopsy and the expertise of the pathologist. Heart damage is a major determinant of survival, and staging with cardiac biomarkers guides treatment⁵⁰.

2.6 Small fibre neuropathy

Small fibre neuropathy presents with length dependent burning pain beginning in the feet where it usually remains worse. Symptoms are worse at night where they can disturb sleep initiation and maintenance resulting in fatigue and increased daytime pain. Patients typically report exposing their feet from their bedclothes, placing them on cold surfaces, spraying them with water or immersing them in ice to relieve pain.

The clinical diagnosis is made on the basis of the history as there are few signs. Reflexes are maintained and typically the only signs are a length dependent sensory alteration to pinprick or temperature. Investigations to prove small fibre involvement are quantitative sensory tests and skin biopsies stained for epidermal nerve fibres which can be quantified in microscopy.

In this setting, evidence-based justification for treating an associated WM or MGUS is lacking. Treatment is usually symptomatic with tricyclic antidepressants, newer SSRI/SNRI drugs, opioids and gabapentinoids.

3. Clinical Outcome Measures

Historically, outcome measures have focused on measures of impairment (strength and sensation based on manual muscle strength and sensory testing) and disability, using classical test theory derived scales.

For strength impairment, individual muscles are given a score of 0 (paralysis) to 5 (normal). The Medical Research Council (MRC) sum score sums the scores of 6 pairs of muscles to represent the overall strength of a patient. The motor component of the Neuropathy Impairment Score (NIS) developed at the Mayo Clinic is very similar⁵¹. Sensory scores, including the Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (ISS) and Neuropathy Impairment Sensory score (NIS_{sens}) are similarly used to capture the sensory status of a patient⁵².

Disability measures have been developed for inflammatory neuropathies, and the overall neuropathy limitations score (ONLS)⁵³ is the standard measure for FDA licensing

requirements. These scores, although frequently used are only some of the 130 or more neuropathy outcome scores that have been used in clinical trials with a significant number in IgM paraproteinaemic neuropathy trials⁵⁴. Disability measures more accurately reflect meaningful change in a patient's condition. For the non-neurologist, rapidly performed, reliable, simple and responsive outcomes are the key to collecting data from the maximum number of patients in clinical practice and trials of new therapies.

Rasch Theory-built scales linearly reflect patient function over the whole range of abilities and can be designed and validated for individual diseases. The Inflammatory Rasch-Built Overall Disability Scale (I-RODS) designed as part of the Peripheral Neuropathy Outcome Measurement Standardisation (PeriNomS) study⁵⁵⁻⁵⁷ fulfils the requirements of a valid and simple disability scale for inflammatory neuropathies which catching meaningful changes over time. It is not completely ideal for patients with IgM MGUS paraproteinaemic neuropathy and a new more responsive scale is currently being developed⁵⁸.

For clinical trial purposes the definition of a core set of outcomes has not been finalised because of the requirement for a responsive Rasch Built Score⁵⁷, as well as the need for measures of ataxia, tremor and quality of life currently under development.

Recommendations:

- *The I-RODS more often captures clinically meaningful changes over time, with a greater magnitude of change, compared with the INCAT-ONLS disability scale and its use is therefore suggested in future trials involving patients with inflammatory neuropathies.*

4. TREATMENT OPTIONS

Once the diagnostic evaluations are completed, there may or may not be a causative link established between the PN and the monoclonal gammopathy. If there is a causative link, then a decision is needed regarding the need or not for treatment. As with smouldering lymphoproliferative disorders, intervention is not always required; for patients with non-progressive neuropathies, even those with a strong likelihood of being linked to smouldering WM, the option of *no treatment* should be considered. The presence of a symptomatic lymphoproliferative disorder will in its own right mandate the institution of therapy. If there is a causal link between the lymphoproliferative disorder and the PN, an improvement or at least stabilisation in the PN might be expected as a helpful by-product of treating the clonal population, provided neurotoxic agents have been avoided.

The presence of a progressive neuropathy in the setting of MGUS or asymptomatic lymphoproliferative disorder may require therapy to arrest or abrogate the PN even though the monoclonal disease burden is not high.

4.1 IgM MGUS-associated PN (Without anti-MAG antibodies)

A number of studies of anti-MAG negative IgM-associated PPN have been reported. In general, response to immunotherapy approaches including intravenous immunoglobulin (IVIg), corticosteroids, plasma exchanges, or a combination of the two, is poor in IgM-PPN of the DADS-IgM phenotype compared to idiopathic CIDP (and the entity referred to as non-IgM-DADS)^{59,60}. Although short-term improvement has been shown, no long term benefit has been shown for IVIg in IgM MGUS-associated PN.^{61,62} Other agents including chlorambucil have not been pursued because of toxicity and lack of perceived effect. There is no effect of interferon-alpha in a randomised controlled trial.^{63,64}

Recommendations

- *In patients without significant disability or haematological reason for treatment, there is no indication for immunosuppressive or immunomodulatory treatment. Symptomatic treatment for tremor and paraesthesia should be offered, and reassurance that symptoms are unlikely to worsen significantly for years.*
- *In patients with significant chronic or progressive disability associated with an IgM MGUS paraproteinaemic neuropathy, immunosuppressive or immunomodulatory treatment may be considered. Although these approaches have not been tested prospectively, in patients with rapid worsening neuropathy, especially when CIDP-like, IVIg, steroids or plasma exchange are recommended to prevent irreversible disability.*
- *In patients unresponsive to IVIg, steroids or plasma exchange, agents such as rituximab, cyclophosphamide with prednisolone, fludarabine, and chlorambucil should be considered after discussion with a neurologist/haematologist.*

4.2 Anti-MAG antibody-associated PN

A Cochrane Systematic Review summarises the evidence for treatments of IgM anti-MAG neuropathy⁶⁵. IVIg may have some benefit in the short term (timescale of weeks) only, but this is of little clinical use. Corticosteroids alone are not effective²⁹, but may be beneficial in combination with other agents such as cyclophosphamide⁶⁶. The purine analogues, fludarabine and cladribine, have demonstrated a modest improvement in some studies^{67,68}, and though tolerance of these agents was reported as good, the studies were small. For occasional patients with rapidly worsening neuropathy especially with signs of motor disability, combinations of active agents or even high dose therapy have been attempted.

There are several non-randomised studies of Rituximab in anti-MAG-associated PN⁶⁹⁻⁷², many reporting positive benefit in small groups of patients. Five studies reported a worsening of the PN following Rituximab⁷³⁻⁷⁷. In the largest report of deterioration⁷⁴ (10 patients) worsening was acute and severe, and occurred during the treatment period. All the patients improved after deterioration but at final evaluation only one improved

compared to baseline, five worsened and four stabilized. Deterioration was not clearly associated with an increase of the anti-MAG antibody titre.

Two randomised controlled trials of rituximab have been negative in their primary outcome measures, but the trials were both underpowered and the outcome measures inadequate (see above).^{78, 79} Secondary outcome measures including patient global impression of change were positive. In meta-analysis the primary outcome measure becomes positive and rituximab appears to be effective (Lunn et al, 2015 Cochrane Systematic Review Update, in press).

Factors predictive of a response to rituximab in anti-MAG neuropathy remain to be elucidated. It is suggested that short disease duration (less than 2 years and certainly less than 5 years), active progression at assessment and preservation of nerve density in biopsies might predict response.⁸⁰ Antibody titres and levels of IgM paraprotein are neither related to the severity of neuropathy nor predictive of response to treatment. It has been suggested that a significant drop in antibody titres might be necessary to achieve a response but the depth of any haematological remission required is not known⁸¹. Stability rather than improvement is the most likely outcome of treatment although rare dramatic improvements are reported.

Recommendation:

There is low quality evidence that rituximab is of benefit in the treatment of anti-MAG demyelinating peripheral neuropathy. The standard dose of 375mg/m² administered weekly for 4 weeks has been used in most studies. There are no clinical indicators to guide the selection of patients for treatment. Measurably progressive disease causing disability is an indication to consider definitive treatment given earlier (<2 years from onset where possible) rather than later is recommended.

4.3 Waldenströms-associated PN

The criteria for the initiation of therapy in symptomatic WM are well established³ and include PN due to WM. The decision to treat and the choice of treatment approach depends on the haematological disease burden and the nature, course and effect of the PN.

There are no trial data specifically assessing the efficacy of treatment options in WM-associated PN. Treon et al reported on the incidence, characteristics and treatment outcome of disease-related PN in 900 WM patients; of these, 199 had disease-related PN, of which 122 patients were evaluated for antibodies to known peripheral nerve epitopes and were found to be positive for MAG in 24.5%, GM1 in 1.64% and sulfatide antibodies in 0.81%⁸⁰. Thirteen of 61 (21.3%) patients examined for amyloid were positive. The median time to treatment for all PN patients was 9 months. Among non-amyloid related PN patients who received plasmapheresis as their first intervention, 69% had symptomatic

improvement whereas 12.5% of those who received IVIG experienced improvement. 151 PN patients received chemotherapy comprising an oral alkylator, purine analogue or rituximab; or rituximab combination / purine analogue combination, cyclophosphamide, thalidomide or bortezomib. Of these, 71 (47%) had improvement and 8 (5.3%) had complete resolution of PN following therapy. Symptomatic improvement was more likely with non-amyloid related PN, in patients who achieved a major response (that is $\geq 50\%$ reduction in serum IgM), those who received therapy within 24 months and those who received rituximab combination vs. any monotherapy vs. rituximab alone.

Avoidance of neurotoxic agents is important, although the speed of response to proteasome inhibitor-containing therapy will need to be weighed against the risk of worsening the PN. Alternative dosing strategies such as weekly dosed bortezomib or second generation agents like Carfilzomib show promise in this regard^{82, 83}. Ibrutinib has shown symptomatic improvement in WM associated PN that progressed after Rituximab and could also be considered⁸⁴.

Recommendations:

- *Where treatment is required, single agent Rituximab, combination immunochemotherapy with Dexamethasone, Cyclophosphamide and Rituximab (DRC), Bendamustine-Rituximab (BR), the Carfilzomib, Rituximab, Dexamethasone (CARD) regimen or purine analogues combinations are possible options that provide appropriate intensity to remit both the systemic disease and the neurological consequences as required.*
- *Ibrutinib, where available could be considered in the setting of intolerance of chemotherapy-based therapies or if previous therapies fail.*
- *The depth of response needed to achieve an optimum outcome remains to be established. In chronic, long-standing PN axonal degeneration has often followed longstanding demyelination and any improvement typically occurs very slowly if at all; a valid goal is to prevent symptomatic deterioration.*
- *Avoidance of neurotoxic agents is important; the vinca alkaloids have no place in the management of WM, particularly those with PN. The speed of response to proteasome inhibitor-containing therapy will need to be weighed against the risk of worsening the PN.*
- *Plasmapheresis⁸⁵, corticosteroids and IVIG are of little or no value⁸⁰ in the treatment of WM-associated neuropathies.*
- *Patients with slowly progressing WM or PN do not require immediate therapy.*

4.4 CANOMAD

Having excluded alternative, infiltrative causes of cranial nerve abnormalities have been excluded, an immunomodulatory approach to treatment is appropriate. There have been

no randomised clinical trials in this setting, but clinical improvement has been noted following IVIG and Rituximab⁸⁶.

Recommendations:

None specific; each case must be treated on its own merit following discussion between haematologist and neurologist

4.5 AL Amyloidosis

Measures to suppress the clone responsible for the production of the amyloid protein are essential and urgent. The intensity of the therapy offered depends on the severity of cardiac and renal involvement of the patient. Where possible, depending on the organs involved and performance status, high dose therapy and autologous stem cell transplantation is the treatment of choice, resulting in a 53% 10-year survival for those achieving a complete response⁸⁷. For stem cell transplant ineligible patients (the majority at 75-80%), upfront therapy with Melphalan-Dexamethasone⁸⁸ or bortezomib-based combinations has proven effective⁴⁵. For relapsing patients, Lenalidomide^{89, 90} and Pomalidomide⁹¹ are recommended. Bortezomib needs to be administered with particular caution due to neurotoxic potential, which can be minimised by subcutaneous administration and weekly scheduling. There is minimal evidence for the effect of Carfilzomib in this setting and ongoing concerns about the possible cardiotoxicity⁹².

Recommendations

Treatment of AL amyloidosis should be risk-adapted and response tailored. Conventional or high-dose alkylator-based chemotherapy is effective in almost two-thirds of patients. Conventional standard therapy is melphalan-dexamethasone; however combinations of bortezomib, dexamethasone, and alkylators achieve higher response rates. The neurotoxicity of bortezomib must be carefully considered. Immune-modulatory drugs are a good option for refractory/relapsed patients.

5. MODELS OF CARE

The wide-ranging clinical entities that comprise IgM-associated PNs are managed in a variety of clinical settings, often by multidisciplinary specialists. In order to achieve successful outcomes for these patients, joint working across disciplines offers a favourable approach that should overcome the barriers of specialists working in isolation and risking a failure to embrace the bigger picture, both in terms of the diagnostic pathway as well as timely and appropriate therapeutic and supportive measures. The main categories are Haematology and Neurology, but specialist nursing care and neurorehabilitation teams

are highly valuable. Each comes to the patient with appropriate knowledge but perhaps limited experience of complex cases. This risks allowing the patient to ‘fall between two stools’ and miss out on the appropriate requesting and interpretation of investigations.

Timely identification, investigation and treatment of patients with PPNs will improve their outlook by limiting misdiagnoses, inappropriate treatments and irreversible neurological damage.

Physical and occupational therapists play a vital role in helping individuals improve and maintain functions that may be limited by PN including exercise intervention to help improve strength and physical function⁹³, balance and coordination activities which can help decrease the risk of falling⁹⁴. A randomised controlled trial of a tailored home exercise programme versus usual care showed that tailored home exercise is acceptable to individuals with inflammatory neuropathies and was associated with significant improvements in activity limitation, fatigue, quality of life and mood⁹⁵. In addition, patient education can focus on improving safety, preventing further complications, and finding alternative ways to perform certain tasks. Timely intervention is recommended in order to maximise functional potential and minimise clinical risk in patients who are significantly functionally impaired.

Provision of appropriate and well-fitting orthotic supports, such as the ankle-foot orthosis (AFO) which provides adjustability of initial ankle angle at which the heel strikes the ground, amelioration of ankle stiffness, improved push-off by providing plantarflexion moment as well as harvesting energy from gait⁹⁶. Such interventions can make a significant functional contribution to patients affected by peripheral neuropathies and is highly recommended.

Recommendations:

- *A suggested model of care is a combined neurological and haematological clinic, in which patients are seen jointly by a specialist neurologist and Haematologist and a decision can be made about the relevant sequence of investigations, their interpretation and the formulation of a treatment plan.*
- *Appropriate referral to physical, occupational and orthotic professionals is recommended in order to maximise safety and function.*

6. FUTURE PERSPECTIVES

Peripheral neuropathies associated with Waldenström macroglobulinaemia and IgM monoclonal gammopathies have a heterogeneous pathogenesis and better understanding of the mechanisms of disease will open new therapeutic avenues. A number of biological agents are currently under investigation in WM, which may prove particularly

suites to the treatment of patients with paraproteinaemic neuropathies, given their non-neurotoxic side effect profiles. It is important for such agents to be explored further in this subgroup of patients, particularly where the burden of tumour cells is relatively low. Such agents are likely to permit a more subtle therapeutic effect, without typical chemotherapy-related side effects, which can be particularly harsh in the setting of a disabling neuropathy where performance status is limited not by the burden of the underlying disease, but the consequence of neural damage.

Proteasome inhibitors (PI) are potent agents that target cell proliferation and survival in B-cell malignancies including WM. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome and in combination with dexamethasone and rituximab produces an ORR of 85-96%^{97, 98}. However, 39% and 30% of patients had grade 2 and 3 PN, respectively in one study and PN occurred in almost half of patients in the other. Although the rate and severity of PN are lower when bortezomib is administered weekly, it is clear that this agent is best avoided in the setting of pre-existing PN. Carfilzomib is an irreversible tetrapeptide epoxyketone PI that binds to active sites of the 20S proteasome, but is structurally distinct from bortezomib. A Carfilzomib/rituximab/dexamethasone combination was assessed in a phase II trial of 31 patients with newly diagnosed WM⁸³. The ORR was 87% and responses were not affected by *MYD88* and *CXCR4* mutation status. Unlike bortezomib, carfilzomib is associated with a low risk of neurotoxicity. Ongoing early phase clinical trials for WM include those evaluating Oprozomib, an orally administered epoxyketone PI (phase I/II, relapsed WM, NCT01416428); Ixazomib, an orally administered boronate PI, in combination with dexamethasone and rituximab (phase II, previously untreated WM, NCT02400437 and phase I/II in previously treated patients).

The PI3K/Akt/mTOR signaling pathway regulates cell survival and the migration of lymphocytes in WM⁹⁹. Several agents that inhibit this pathway have shown to be effective in the clinical trial setting. In a phase II trial of 33 patients with newly diagnosed WM, Everolimus, an oral mTOR inhibitor, was administered until disease progression or unacceptable toxicity¹⁰⁰. The ORR was 72% and grade ≥ 2 adverse events at least partially Everolimus-related included anemia, rash, oral ulcerations, and neutropenia but not PN. Although not currently endorsed by treatment guidelines for WM, Perifosine, an inhibitor of Akt, has shown antitumor activity in preclinical and clinical studies of WM¹⁰¹. In a phase II study of 37 patients with relapsed and/or refractory WM, Perifosine monotherapy was associated with an ORR of 35%. The most commonly observed adverse events were gastrointestinal disorders, fatigue, and cytopenias.

Bruton's tyrosine kinase (BTK) is a component of the B-cell receptor signaling pathway and has been implicated in WM development and the *MYD88L265P* mutation has been shown to act upstream of BTK and increase the activity of BTK signaling¹⁰². In a phase II trial of 63 patients with relapsed or refractory MM, patients received the BTK inhibitor

ibrutinib until disease progression or unacceptable toxicity. Patients achieved an ORR of 90.5% and a major response rate of 73%¹⁰³. Based on these data, the US Food and Drug Administration approved ibrutinib for the treatment of WM and the European Commission approved ibrutinib for the treatment of patients with WM who have received at least one prior therapy, or as first line treatment for patients unsuitable for chemo-immunotherapy. Other agents currently in clinical trials include ACP 196, a novel BTK inhibitor (phase I, NCT02180724) and IMO-8400, an oligonucleotide specifically designed to inhibit toll-like receptor signaling pathways, for which MYD88 is a key linker protein (phase I/II, relapsed/refractory WM, NCT02092909).

Daratumumab, a humanised antibody to CD38, has also shown encouraging responses in a percentage of refractory patients in Phase I and II trials, both as a single agent and in combination¹⁰⁴. Monoclonal antibody-based therapy in Waldenström macroglobulinemia (WM) has traditionally targeted the B cell component. The heterogeneity in surface expression seen could potentially affect efficacy of antibody treatment and clonal plasma cells in WM have significant levels of surface expression of CD38¹⁰⁵. Following the encouraging results shown in the myeloma setting, the expression data suggest that Daratumumab may also be highly effective for eradication of the plasma cell component of WM and may be particularly suited to those instances when the clinical features are a consequence of the M protein such as hyperviscosity and neuropathy.

Phosphatidylinositol 3-kinase (PI3K) is a lipid kinase; in B lymphocytes, the δ isoform (PI3K δ) plays a central role in normal B-cell development and function, transducing signals from the B-cell receptor as well as from receptors for various cytokines, chemokines, and integrins. PI3K δ signalling pathways are commonly hyperactive in B-cell malignancies, making inhibition of PI3K δ a promising target in the therapy of indolent lymphomas like WM.

Idelalisib is a potent, small-molecule inhibitor of PI3K δ that is highly selective for the δ isoform and blocks PI3K δ /AKT signalling and promotes apoptosis. In a phase I study in 64 patients with relapsed indolent non-Hodgkin lymphoma, Idelalisib induced a response in 46/54 (85%) of evaluable patients achieving an overall response rate of 30/64 (47%)¹⁰⁶. The median duration of response was 18.4 months, median progression-free survival was 7.6 months. Idelalisib is well tolerated with no reported incidence of neuropathy as a side effect.

CONCLUSIONS

There is much to be done to improve outcomes for patients with IgM and Waldenström-associated peripheral neuropathies. Starting with early recognition of the problem, appropriate causal attribution achieved through sensitive diagnostics which are not

overly invasive, timely therapeutic intervention with effective therapies, achievement of an appropriate degree of clonal reduction for optimum clinical outcomes and the use of reproducible and readily applicable tools to measure outcomes. Importantly, clinical trials of emerging therapies are urgently needed in this clinical setting.

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