Waldenstrom’s 101 & WM in the UK

OCTOBER 27, 2018
EDUCATIONAL FORUM

Dr Shirley D’Sa, UCLH Centre for WM and Related Conditions
What is Waldenström's Macroglobulinaemia?

- Anti MAG Neuropathy?
- IgM MGUS?
- Myeloma?
- Lymphoplasmacytic lymphoma (LPL)?
- Non Hodgkin's Lymphoma?
- Paraprotein? Immunoglobulins?
- Waldenstrom’s Macroglobulinaemia (WM)?
- Bing Neel Syndrome?
A Good Place to Start...

Lymphoma

Multipotent hematopoietic stem cell (Hemocytoblast)

Common myeloid progenitor
- Erythrocyte
- Mast cell
- Myeloblast

Common lymphoid progenitor
- Natural killer cell (Large granular lymphocyte)
- Small lymphocyte
- T lymphocyte
- B lymphocyte

Megakaryocyte
- Thrombocytes

Basophil

Neutrophil

Eosinophil

Monocyte

Macrophage

Plasma cell
Under the Microscope... (bone marrow smear)
What do lymphocytes and plasma cells do?

- Produce different types of antibodies or immunoglobulin (IgG, IgA, IgD, IgE, IgM)
- Response to infection and critical part of the immune system
- In WM are constantly being made without need
- Can be measured as the paraprotein if from a specific cancer cell

LARGE MOLECULES--IgM circulates as pentamers= groups of 5
What is a paraprotein?

Healthy plasma cells → Various antibodies → Fight Infections → Cause problems

WM Plasma cells (cancer cells)

One variety (monoclonal) of antibody = M-protein = Paraprotein
Detecting a paraprotein: SPEP
Symptoms of WM
Major Components

Abnormal cell growth

- Lymphoma
- Low red cells (anaemia)
- Low platelets (bleeding)
- Low neutrophils (Recurrent infections)
- Lymphadenopathy, splenomegaly, CNS
- Weight loss

Abnormal protein production

- Paraproteinaemia
  - Hyperviscosity
  - Peripheral neuropathy
  - Haemolysis (destruction of red cells)
  - Amyloidosis
  - Cryoglobulinaemia
  - Clotting problems
Low Red Cells: Anaemia

>>Reduced Oxygen to Tissues

- Fatigue
- Breathless
- Exercise tolerance
- Dizziness
- Palpitations
- Pounding in ears
- Looking pale
Paraprotein-related symptoms

Each paraprotein has unique:
- Physical properties
- Binding properties

- Hyperviscosity
- Cryoglobulinaemia
- Auto-antibodies
- Amyloid
- Bleeding Problems

Dimpopoulos Blood 1994
Hyperviscosity syndrome (HVS)

Symptoms:
- Fatigue
- Headaches
- Blurred Vision
- Bleeding gums & nose
- Confusion

- 15%-40% patients
- Likely if plasma viscosity >5 mPa (normal range 1.4-1.8 mPa)
- Increased risk
  - IgM > 50 g/L
  - Vascular Risks

Normal

HVS

Ghobrial haematology 2012
Autoantibody activity = activity against self

Cold Agglutinin Disease

Red Blood Cell

Myelin (MAG)

Neuropathy

Schnitzler syndrome

Cryoglobulins (type II)
Cold activity

- Cold agglutinin disease (CAgD)
  - ‘Cold’ haemolysis - red cell breakdown (anaemia and dark urine)
- Cryoglobulinaemia
  - Potential damage to kidneys, joints, skin, circulation, nerves

Acrocyanosis

Raynaud’s syndrome
Neuropathy: nerve damage

Peripheral
24% patients

- Symptoms
  - Tingling or numbness
  - Abnormal sensation
  - Weakness arms & legs
  - Loss of reflexes
  - Fatigue

Autonomic

- Symptoms
  - Constipation or diarrhoea
  - Dizziness on standing
  - Bladder problems

Causes
- Anti-myelin associated Glycoprotein Ab (MAG)
- Amyloidosis
- Cryoglobulinaemia
AL Amyloid- deposition of misfolded light chains (kappa or lambda) >> results in progressive tissue damage

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Heart</td>
<td>74 %</td>
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<tr>
<td>Kidney</td>
<td>74 %</td>
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<tr>
<td>Nephrotic</td>
<td>74 %</td>
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<tr>
<td>Liver</td>
<td>74 %</td>
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<tr>
<td>Gut</td>
<td>74 %</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>17 %</td>
</tr>
<tr>
<td>ANS</td>
<td>14 %</td>
</tr>
<tr>
<td>PNS</td>
<td>15 %</td>
</tr>
<tr>
<td>WM patients</td>
<td>&lt; 5 %</td>
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</tbody>
</table>

Modified from Merlini G, Blood 2012;119:4343-4345
AL Amyloid- deposition of misfolded light chains (kappa or lambda) >>results in progressive tissue damage

IMPORTANT TO CONSIDER THE POSSIBILITY OF AMYLOIDOSIS

REQUIRES A MODIFIED APPROACH TO TREATMENT WITH DIFFERENT GOALS
Bleeding and bruising in WM

- **Platelets**
  - Production reduced
  - Immune destruction (ITP)
  - Impaired function

- **Clotting factors**
  - IgM interference
  - Acquired hemophilia
  - Acquired von Willebrand’s disease (vWD)

Dimopoulos Blood 1994
Perkins Blood 1970
Diagnosis of WM
Bone marrow biopsy to assess the cellular burden
Black and Decker version
Radiology - to assess lymph nodes and spleen
MGUS (Monoclonal gammopathy of uncertain significance) vs Smouldering WM vs Symptomatic WM

- Presence of IgM paraprotein in blood

- = IgM Monoclonal gammopathy

- (MGUS)

  - 3% in the >70 years; 5% in >80 years

- Results from a gradual accumulation of clonal cells* in the bone marrow

- If asymptomatic, **not** affecting organs or rapidly changing then **no need for intervention**

*One of a kind
MYD88 etc.
In WM, the most common mutation occurs in MYD88 gene.

Over 90 percent of patients carry this mutation in the WM cells.

MYD88 L265P mutation turns on growth and survival pathways including Bruton tyrosine kinase (BTK), the target of ibrutinib.

There are other mutations (not L265P) that confer similar characteristics.
The second most frequently mutated gene in WM is **CXCR4**, which occurs in about 30-40% of cases.

Almost exclusively present in MYD88-mutated WM

Mutations of this gene, which are known to play a key role in the trafficking of immune cells in the body

In WM, mutations of **CXCR4** turn on growth and survival pathways

WM cells with some mutations of the CXCR4 gene also show resistance to Ibrutinib
When to treat WM?
Not everyone needs treatment

- Smoldering Waldenström’s Macroglobulinaemia (SWM) is an intermediate state in which the IgM monoclonal protein is ≥ 30 g/L and/or a bone marrow contains ≥ 10% LPL cells.

- These patients may progress to symptomatic WM, amyloidosis or lymphoma at a rate of 6% in the first year, 39% at 3 years, 59% at 5 years and 68% at 10 years.

**Indications for treatment (guide for doctors)**

Progressive symptoms and diminished patient well-being should be the trigger

**Not specific cut-off of IgM**

<table>
<thead>
<tr>
<th>Clinical indications</th>
<th>Laboratory indications</th>
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<tbody>
<tr>
<td>Signs and symptoms associated with hyperviscosity</td>
<td>Hemoglobin &lt;10 g/dL</td>
</tr>
<tr>
<td>Moderate to severe peripheral neuropathy</td>
<td>Platelet count &lt;100×10⁹/dL</td>
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<tr>
<td>AL amyloidosis</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Symptomatic cryoglobulinemia</td>
<td></td>
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<tr>
<td>Constitutional symptoms, Raynaud’s phenomenon, and arthralgia</td>
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<tr>
<td>Bulky or symptomatic lymphadenopathy</td>
<td></td>
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<tr>
<td>Symptomatic organomegaly</td>
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<tr>
<td><strong>Abbreviation</strong>: AL, amyloid light-chain.</td>
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# Key issues regarding treatment

<table>
<thead>
<tr>
<th>When to treat</th>
<th>Objectives</th>
<th>How to treat</th>
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<tbody>
<tr>
<td>LPL cells have accumulated excessively in BM causing anaemia</td>
<td>Take back control of bone marrow</td>
<td>Intensively enough to do the job without excessive toxicity</td>
</tr>
<tr>
<td>LPL cells have expanded lymph nodes and spleen or extramedullary sites</td>
<td>Shrink abnormally enlarged tissues and organs</td>
<td>Intensively enough to do the job without excessive toxicity</td>
</tr>
<tr>
<td>resulting in consequences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM is causing symptomatic high blood viscosity</td>
<td>To lower IgM level as soon as possible</td>
<td>Plasma exchange and treatment that works rapidly</td>
</tr>
<tr>
<td>IgM is causing immunological spin-offs such as neuropathy, cold agglutinin</td>
<td>To neutralize the activity of the rogue antibody</td>
<td>Ideally more subtle treatment that produces a complete response</td>
</tr>
<tr>
<td>disease</td>
<td></td>
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In all cases....

<table>
<thead>
<tr>
<th>REMEMBER THE TREATMENT OBJECTIVES</th>
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<tbody>
<tr>
<td>Fitness of patient</td>
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<tr>
<td>Wishes of patient</td>
</tr>
<tr>
<td>Minimise toxicity/ burden of treatment</td>
</tr>
<tr>
<td>Maximise benefit of each treatment</td>
</tr>
<tr>
<td>Use treatments judiciously</td>
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<tr>
<td>Don’t give unnecessary treatment</td>
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Chemotherapy + Rituximab (finite number of weeks) vs Continuous therapy e.g. Ibrutinib

Add maintenance for deeper effect?

Orderly and appropriate sequence

Too much treatment increases the risk of infections
## How to measure response to treatment?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Complete Response</strong></td>
<td>CR</td>
<td>Disappearance of monoclonal protein by immunofixation, no histological evidence of bone marrow involvement, and resolution of any adenopathy / organomegaly (confirmed by CT scan), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required at least 6 weeks apart with a second immunofixation.</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>PR</td>
<td>A ≥50% reduction of serum monoclonal IgM concentration on protein electrophoresis and ≥ 50% decrease in adenopathy/organomegaly on physical examination or on CT scan. No new symptoms or signs of active disease.</td>
</tr>
<tr>
<td><strong>Minor Response</strong></td>
<td>MR</td>
<td>A ≥ 25% but &lt; 50% reduction of serum monoclonal IgM by protein electrophoresis. No new symptoms or signs of active disease.</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>SD</td>
<td>A &lt;25% reduction and &lt;25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>PD</td>
<td>A ≥25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥ 38.4°C, drenching night sweats, ≥ 10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.</td>
</tr>
</tbody>
</table>
Special situations: involvement of the nervous system
Nerve damage: peripheral neuropathy

- Neuropathies associated with IgM paraprotein present variously as
  - Anti-MAG mediated peripheral neuropathy
  - Peripheral neuropathy without anti-MAG antibodies
  - IgM-associated peripheral neuropathy with ganglioside antibodies

- Although there are aspects of these disorders that are distinct, the symptoms are often similar
Assessing Neuropathy

- Nature of symptoms, spatial distribution
- Speed of onset
- Rate of change
- Effect on functional abilities
- Motor/ sensory/ autonomic features

- Examination to confirm neurological picture and provide a baseline for future comparison
  - Features of amyloid- bruising, oedema, cardiac insufficiency, postural drop in BP
  - Features of cryoglobulins- acrocyanosis, livedo reticularis, ulcers

- Examination to confirm haematological picture: MGUS vs WM
  - Lymphadenopathy
  - Splenomegaly
MAG is a glycoprotein localised in “Schwann cells” on the innermost myelin wrap, directly across from the axon surface.

Some IgM antibodies target MAG and damage the insulation (myelin sheath) of the nerve fibre (axon).
Investigations
Anti-MAG neuropathy treatment: Who, when, what for

- Only if there is a progressive functional impact: case-by-case decision
- Short disease duration (<2 years), active progression at time of treatment might predict response\(^1\).
- The depth of optimal haematological remission is not known\(^2\).
- Complete elimination of the clonal IgM is probably not practical or possible.
- Stability rather than improvement is the most likely outcome of treatment

1. Treon SP 2010
2. Benedetti et al 2007
Anti-MAG neuropathy
Therapeutic options

**IVIG** may have limited benefit in the short term (timescale of weeks)

**Purine analogues** (*Fludarabine and Cladribine*) have demonstrated a modest improvement in some studies, and although tolerance of these agents was reported as good, the studies were small\(^3,4\).

**Steroids** alone are not effective, but may be beneficial in combination with other agents such as **cyclophosphamide**.

For occasional patients with rapidly worsening neuropathy especially with signs of motor disability, **combinations of active agents** or even high dose therapy and **stem cell transplantation** have been attempted.
Anti-MAG neuropathy: **Rituximab**

- There are several non-randomised studies of Rituximab in anti-MAG-PN reporting positive benefit in small groups of patients.

- Five studies reported a worsening of the PN following Rituximab, possibly related to an IgM flare.

- Two RCTs of Rituximab have been negative in their primary outcome measures.

- Secondary outcome measures including patient impression of change were positive and a systematic review highlights significant therapeutic benefit.

- Factors predictive of a response to Rituximab in anti-MAG-PN remain to be elucidated.
Bing Neel syndrome

Definition

Infiltration of WM cells in the central nervous system.
Who gets BNS?

- ≈ 1% of all WM patients
- Lack of clinical awareness, under-reporting?
- No prospective studies, ±150 pts reported in literature
  - 2 publications with 34 and 44 pts, respectively
- Can be presenting symptom of WM ≈ 15-36%
- Can be present without any other evidence of active/progression of systemic WM

Simon et al, Haematologica 2015, 1587-1594
Castillo et al, Br J Haematol, 2016, 709-15
BNS in patients with known WM: pitfalls!

- The median time from WM to BNS diagnosis was 3 and 8.9 years (range 0 to 24.7 years).

- For 71% of the 28 patients previously diagnosed with WM, BNS occurred independently of a systemic progression of WM.

- At the time of BNS diagnosis, seven patients were actively receiving therapy, of which six were responding to their current therapy based on serum IgM level reduction.

Simon et al, Haematologica 2015, 1587-1594
Castillo et al, Br J Haematol, 2016, 709-15
Clinical picture is extremely variable without any specific signs or symptoms

- Altered mental status, including memory loss
- Cranial nerve disorder
- Paraplegia/paralysis
- Unsteady gait

- Headache
- Paresthesia
- Seizures
- Limb pain

- Psychiatric symptoms
- Blurry vision
- Hearing loss
Suspected BNS: Step 1

Consult neurologist
  • Alternative explanation?

Important to mention Bing Neel Syndrome as an option
Step 2: Radiology = MRI

<table>
<thead>
<tr>
<th>Radiological findings</th>
<th>Prevalence of radiological findings (N and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptomeningeal involvement</td>
<td>17/24 patients or 70.8%</td>
</tr>
<tr>
<td>Dural involvement</td>
<td>9/24 patients or 37.5%</td>
</tr>
<tr>
<td>Parenchymal involvement</td>
<td>10/24 patients or 41.7%</td>
</tr>
</tbody>
</table>

Imaging spectrum of Bing–Neel syndrome: how can a radiologist recognise this rare neurological complication of Waldenström’s macroglobulinemia?
Step 3: lumbar puncture > cerebrospinal fluid (CSF)

- CSF analysis;
  - Cell count (lymphocytosis)
  - Morphology
  - Total protein
  - Flow cytometry
  - Molecular testing
    - $MYD88^{L265P}$ mutation
    - VDJ rearrangement
  - Protein electrophoresis and immunofixation
- Brain or meningeal biopsy is rarely required
Therapy for BNS: CNS penetrating chemotherapy

**Methotrexate**
- \( \geq 3 \text{ g/m}^2 \): cytotoxic conc in CSF, > 1 g/m2 in brain parenchyma, blood-CSF conc. 30:1

**Cytarabine**
- Intermediate to high dosing \( \geq 2 \text{ g/m}^2 \)

**High dose intensive schemes as used in primary CNS lymphoma**

**Purine analogues**
- Fludarabine
- Cladribine
- Bendamustine
- Pass blood brain barrier
- Can be damaging to nerves

**Targeted Therapy**
- BTK inhibitors cross the blood brain barrier
- Higher doses may be needed
Welcome to the UK

The Rory Morrison Registry
• WMUK is a unique not for profit organisation, also a registered charity, developed jointly to bring WM patients and medical professionals closer together to improve the treatment of WM
• Medical board of doctors treating WM in the UK together with patient representatives
• Annual WMUK doctor/patient forums
• Point of contact for patients and families
• WMUK is also involved in patient advocacy at UK and EU levels
• We work closely with the IWMF, Lymphoma Action, Myeloma UK
• Develop and maintain links with Pharma companies
WMUK Projects

- Key role to put the UK on the map and participate in clinical trials of novel agents

- With support from patients and families, and that of other bodies such as the IWMF and Pharma we launched an ambitious funding package for
  - the Rory Morrison Registry
  - a Biobank at University College Hospital in London (jointly with the IWMF)
  - sponsorship of a research projects
Rory Morrison Registry (RMR)

• Increasing role for novel therapies in WM
• Important to capture ‘real world data’ to establish the landscape of WM in the UK and to assess the impact of newer treatments
• Funding for the Rory Morrison Registry (RMR) project was made possible by generous donations to WMUK
• Demographics, diagnosis, treatment and patient reported outcomes (PRO)
• The RMR has been acknowledged as a valuable resource by NHS England’s Final Appraisal Determination for Ibrutinib for relapsed/refractory Waldenström’s (2017): IBRUTINIB on CANCER DRUGS FUND (CDF)
The clinical registry of treatment outcomes for those with WM gathers information from any registered UK doctor treating WM so the disease may be better understood and treatment improved. WMUK is a unique charitable alliance of doctors, patients, nurses and carers fighting WM. The Registry is dedicated to the memory of founder member Rory Morrison, the much-loved BBC Radio 4 broadcaster who died in 2013. His former BBC colleague Charlotte Green is our Patron.

The WM Registry has already received generous grant funding from the following, but more funding is welcome for its upkeep.
Timeline

• The initial 12 month phase
  • defining the objectives of the Registry
  • designing the structure of the Registry
  • fundraising for the expansion of the Registry

• The second 12 month phase
  • obtaining regulatory and ethical approval
  • development of the data acquisition teams at the registered centres
  • Subsequent successful pilot at UCLH followed national rollout in January 2018
Data in the Registry

• In total 579 patients are currently registered from 19 hospitals; this includes 8 patients who have specifically signed up to the Patient Reported Outcomes extension despite their hospital not yet being registered with the Registry.

• In total 11 centres are formally registered, with 5 centres undergoing registration at present.

• So far 6 centres have regularly entered data; the remaining centres have been hampered by delays in local processing and resource allocation.
Demographics and diagnosis

- Traditionally, WM is perceived as a condition of elderly, Caucasian males.
- Findings from the Registry would suggest that there is a very significant younger population developing WM: over 35% were diagnosed in their thirties, forties or fifties.
- Similarly, the ratio of male: female patients was closer to 1.6:1 suggesting a very significant female population with WM or IgM associated condition.
- 51% of patients presented with symptoms of WM relating to paraprotein production (peripheral neuropathy, hyperviscosity or haemolytic anaemia) or lymphomatous related conditions such as anaemia, lymphadenopathy or B symptoms (fevers, night sweats and weight loss).
- The remaining 49% entered the active monitoring programme (watch and wait).
Treatment

- The time from diagnosis to treatment varies hugely (median 4 months, but ranging from months to years).

- Most strikingly is the variety of treatments (over 26) used as first line therapy and how these have changed with time.
Patients with a diagnosis of WM undergoing second line treatment: Regimen (n=165)

- CHOP
- Fludarabine + Rituximab
- R-CP
- CVP
- DRC x 6 plus 2 Rituximab
- FC
- R-IDARAM
- Stem cell harvest (failed)
- Weekly Cyclophosphamide
- Bendamustine
- Bortezomib + Dexamethasone + Rituximab
- FCR
- IDARAM
- R-CVP
- Chlorambucil + Prednisolone
- Stem cell harvest (successful)
- Autograft stem cell transplant
- Chlorambucil
- ESHAP
- Fludarabine
- Cladribine + Rituximab
- Rituximab x 4
- R-CHOP
- R-ESHAP
- Rituximab alone
- Bendamustine + Rituximab
- DRC
- Other
- BTK Inhibitors

Percentage of patients treated
Outcomes

• Based on the Registry, median overall survival in patients presenting with symptomatic WM is 18.5 years and even longer in asymptomatic patients.

• This needs to be taken in the context of the data limitations, but would suggest a promising outcome for patients with WM, even for those who present symptomatically.

• Complications from WM such as high grade transformation have been noted in the analysis, but other complications, for example recurrent infections or treatment complications, will form part of a more comprehensive analysis of the Registry in the future.
Patient reported outcomes

- Health related Quality of Life (HrQoL) and Patient Reported Outcomes (PRO) are multi-dimensional concepts reflecting the physiological, psychological and social influences of the disease and its treatment from the patient’s perspective.

- Quality of life in WM is of paramount importance due to its chronic relapsing nature, the lack of sufficient information regarding the personal impact of various chemotherapy treatments, and the paradigm shift offered by novel therapies, many of which are administered continuously until progression.

- Since WM is a chronic condition with an unpredictable course, the mental health of patients is of critical importance.

- The Hospital Anxiety and Depression Score (HADS) is a validated method to assess the prevalence of anxiety and depression. Scores between 8 and 10 suggest moderate anxiety and above 10 confirm a diagnosis of anxiety.
The chart below demonstrates results from the HADS questionnaire received from 63 patients through both hand-written forms and online submission. Irrespective of time from diagnosis, anxiety can be present in between 10% and 20% of the population. This significant cohort may benefit from specific referral to cancer support services and psychological support.
• Planned expansion of the Rory Morrison Registry is currently underway to increase the number of centres registered and patients registered for the PRO extension.

• Continued updates to the Registry include capturing treatment complications and the role of supportive care.

• With further data entry and patient/centre registration the Registry will be used as a hypothesis generating tool alongside its surveillance and observational capabilities.

• The Registry is still in its infancy, but this first report demonstrates the potential of a the Rory Morrison Registry to truly capture the ‘real world data’ and understand the landscape of WM in the United Kingdom for the benefit of patients.
Take home messages

- WM is a rare and very varied disease
- Confusing terminology - that confuses patients and doctors
- Most patients are at W+W stage
- Although incurable, generally responds very well to treatment
- Great progress being made with many new treatment options
This work is supported by grants from the International Waldenström’s Macroglobulinemia Foundation (IWMF) and Waldenström’s Macroglobulinaemia United Kingdom (WMUK) and the generosity and support of patients and their families, without who this project would not have been possible.