Introduction

Multiple myeloma is a clonal disorder of plasma cells with overproduction of a monoclonal antibody ('paraprotein' or 'M-protein') by the malignant cells. Myeloma can be classified by the type of antibody that the plasma cells produce; IgG is the most common.
Myeloma accounts for 1% of all cancers and approximately 10% of haematological cancers. The median age at presentation is 70 years. It is generally considered a chronic, relapsing and remitting disease which is incurable. The median overall survival now approaches 6-10 years thanks to the development of new drugs for upfront treatment and relapsed disease, for both fit and frail patients.

Definition

The definition of myeloma as per the International Myeloma Working Group (IMWG):
Clonal bone marrow plasma cells >10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of:

- Hypercalcaemia >2.75mmol/L
- Creatinine >177mmol/L or CrCl <40ml/min
- Hb <100 (or <20g/L below the lower limit of normal)
- Bone lesions – one or more osteolytic lesions on XR, CT or PET/CT ≥5mm in size. More than one focal lesion on MRI ≥5mm in size.

In addition to the typical 'CRAB' (hyperCalcaemia, Renal impairment, Anaemia, Bone lesions) features that indicate symptomatic myeloma, the following additions to the definition of myeloma have allowed treatment of a group of patients at high risk of progression (80% of these patients progress to having CRAB features within 2 years):

- ≥60% clonal plasma cells on bone marrow aspirate
- Serum free light chain ratio ≥100 or <0.01 (provided the involved light chain is at least 100mg/L)

MGUS

Most patients with myeloma progress from an asymptomatic pre-malignant process known as MGUS – monoclonal gammopathy of undetermined significance. Please see MGUS information sheet for more information. MGUS progresses to myeloma at a rate of 1% per year. Patients with MGUS and asymptomatic myeloma require monitoring but no immediate treatment.

Symptoms of Myeloma

Typical symptoms of myeloma are related to the organ damage that the plasma cells and associated paraprotein cause. Lytic lesions can cause bone pain, pathological fractures and spinal cord compression. Anaemia can cause lethargy and shortness of breath. Hypercalcaemia may cause thirst, constipation, low mood and confusion. Rarely patients can present with hyperviscosity (confusion, blurred vision, epistaxis, headaches) due to a high level paraprotein. Alternatively myeloma may be identified on routine blood tests e.g. a new anaemia, kidney injury or raised protein/ globulin level may trigger a clinician to perform protein electrophoresis.

Investigations

Appropriate initial investigations include:

- FBC and blood film – normocytic normochromic anaemia is typical, +/- rouleaux on film review
- U+Es, LFTs, bone profile
- Immunoglobulins, protein electrophoresis and immunofixation
- Serum free light chains or Bence Jones Protein (a measure of light chains present in the urine)
- Albumin, LDH and Beta 2-Microglobulin play a role in prognostication
- The patient should be tested for HIV, Hepatitis B and Hepatitis C prior to commencing multi-agent chemotherapy
- Bone marrow aspirate and trephine biopsy: a cell count on the aspirate is used to determine plasma cell percentage. Flow cytometry (e.g. for the myeloma markers CD38, CD138, CD56 and K / L expression) of the aspirate will be used to confirm that the plasma cell population is clonal. Cytogenetics including FISH will be performed on the bone marrow aspirate to look for poor risk prognostic mutations.
- Skeletal imaging – choice of imaging will depend on local protocols and availability. Whole body MRI is recommended as first line imaging by NICE. Alternatively PET/CT can be used. Whole body low-dose CT is often used for the initial work up of probable MGUS as it is a more accessible form of imaging.
- MRI whole spine will be required if there are concerns about significant vertebral involvement with lytic lesions, or if there are symptoms or signs suggesting cord compression or nerve root compression.

Prognostic scores

Whilst prognostic scoring in myeloma does not necessarily change a patient's treatment approach, it can give important information on expected survival.
Revised international staging system (R-ISS):

- Stage 1 – B2M <3.5, albumin ≥35, standard risk chromosomal abnormalities, normal LDH. Median progression free survival (PFS) 66 months.
- Stage 2 – Not Stage 1 or 3. Median PFS 42 months.
- Stage 3 – B2M≥5.5 and either high LDH or high risk chromosomal abnormalities. Median PFS 29 months.

Treatment

Myeloma is not a curable disease but usually responds well to treatment. The principles of treatment are to achieve remission with anti-myeloma drugs whilst supporting recovery of related organ or tissue impairment, such as bone lesions or kidney impairment. Once in remission, consolidation or maintenance of remission using various therapeutic approaches is desirable in order to achieve long term progression free survival. Patients are encouraged to consider clinical trials where available.

As previously described there are now many treatment options available. Where patient fitness allows / appropriate most clinicians would favour a relatively aggressive multi-agent treatment upfront with the aim of achieving a complete response.

If the patient is fit – guided by performance status, co-morbidities and age (generally <70 years old), then standard of care is induction chemotherapy to achieve remission followed by consolidation with high-dose therapy (HDT) and stem-cell rescue (an autologous stem cell transplant (ASCT). At the time of writing, Induction therapy in the UK typically consists of a three-drug combination (triplet) containing Bortezomib (Velcade®), Thalidomide and Dexamethasone – commonly referred to as VTD. Most patients will respond to triplet combinations. At least 1/3 will achieve a complete response after 4-6 induction cycles. Initial treatment regimens for patients not suitable for HDT-ASCT are commonly multi-agent. There is no gold-standard combination but options typically include combinations of a proteasome inhibitor (e.g. bortezomib), an alkylating agent (e.g. cyclophosphamide), an immunomodulatory drug (e.g. Thalidmoide and Lenalidomide) and steroids (most commonly in the form of dexamethasone). Regimens include:

- Bortezomib, Cyclophosphamide, Dexamethasone (VCD)
- Bortezomib, Dexamethasone
- Cyclophosphamide, Thalidomide, Dexamethasone (CTD)
- Lenalidomide, Dexamethasone

Supportive medication

Patients with myeloma have a compromised immune system.
Aciclovir prophylaxis is given alongside treatment to reduce the risk of certain viral infections and reactivations including herpes zoster.
An antibiotic such as Co-trimoxazole is usually given alongside treatment to reduce the risk of pneumocystis pneumonia (PCP).
Allopurinol is usually given with cycle 1 of induction treatment to reduce the risk of tumour lysis syndrome.
Thromboprophylaxis is also often used because Certain medications carry a thrombotic risk and require risk-adjusted thromboprophylaxis (see 'pitfalls' below)
Bone protection with bisphosphonates (see 'bone disease' below)

Monitoring

Following completion of treatment patients should be monitored at least every 3-4 months. This includes assessment of symptoms relating to myeloma and its treatment and blood tests to monitor for myeloma relapse. Routine monitoring tests will include FBC, UEs, bone profile, immunoglobulins, serum protein electrophoresis and serum free light chains. Imaging will be symptom directed if any new bone pains develop.

Relapsed disease

Treatment of myeloma at relapse is a rapidly expanding field with many novel therapeutic options. Treatment will typically include a combination of drugs using one or more medications that have not been used in prior lines of treatment.
Options include

- anti-CD38 monoclonal antibodies (e.g. Daratumamab and Isatuximab) which cause direct and indirect myeloma cell death (CD38 is a cell marker typically found on plasma cells);
- alternative proteasome inhibitors (e.g. Ixazomib or Carfilzomib);

- alternative immunomodulatory drugs (e.g. Pomalidomide);
- other novel agents, e.g. histone deacetylase inhibitors (e.g. Panobinostat)

A second ASCT may be offered to a patient if they remain relatively fit on first relapse, and if there has been 2 or more years from initial therapy to 2nd line treatment.
If a patient has multiply relapsed they may be considered for novel agents including in a clinical trial.

Bone disease

All patients should receive bisphosphonate treatment (zoledronic acid as first line if eGFR>30). This has a disease modifying effect as well as bone remodelling – it reduces fractures, preserves bone density, prolongs PFS and overall survival (OS). Consider the need for referral for dental assessment prior to bisphosphonate (given the risk of osteonecrosis of the jaw). Bisphosphonates are usually given regularly for the first 2 years after commencing treatment.
Significant spinal disease may require orthotic bracing until bones strengthen with myeloma treatment. Significant spinal/sternal and pelvic disease may mean a patient is put on bed rest or partial weight bearing during initial treatment.
Radiotherapy may be required for fractures where surgery is not appropriate, and when pain is not controlled with chemotherapy and analgesia.
Surgery is very rarely required. Usually the multi disciplinary team (MDT) favours a conservative approach where possible as myelomatous bones are soft and therefore not easily amenable to surgical fixation.

Common pitfalls of myeloma and its treatment

- Light chain-only myeloma can easily be missed; the usual blood result triggers (high globulin etc) may be absent and protein electrophoresis often negative. If myeloma is clinically suspected then do not forget to request the serum free light chains.
- Peripheral neuropathy is a common complication. It is often multifactorial – disease associated (e.g. spinal cord or nerve root compression), M-protein associated (seen more with MGUS than myeloma), comorbidities (diabetes, carpal tunnel, renal failure), chemotherapy (thalidomide – cumulative effect, mild-moderate, usually improves on stopping; bortezomib – can take 2 years to resolve). Chemotherapy may need to be dose-reduced, paused or stopped all together depending on the severity of neuropathy.
- Venous thromboembolism (VTE) – there is a 10% VTE rate in the first 6 months of treatment with thalidomide or lenalidomide. Patients often have multiple risk factors – active cancer, reduced mobility due to bone disease, myeloma therapies (particularly the immunomodulatory drugs). Patients should be risk assessed and consider prophylactic low molecular weight heparin (LMWH). An attenuated dose non-vitamin K oral anticoagulant (NOAC) can also be used e.g. Apixaban 2.5mg BD.
- Cytopenias – anaemia is common at presentation, thrombocytopenia is more common with end stage disease. Lenalidomide can cause issues with myelosuppression; these patients should have a weekly FBC on initiating treatment. Erythropoietin (EPO) may be considered to support the haemoglobin if a patient has

symptomatic anaemia and haematinics have been optimised. GCSF may be used to help support the neutrophil count during treatment.

- Thalidomide and derivatives can cause thyroid dysfunction and bradyarrhythmias - check TSH and an ECG before commencing these treatments.

Supportive care

All myeloma patients are managed with an MDT approach.
Emotional and psychological support for patients should not be forgotten.
Analgesia should be given for bone pain due to lytic lesions as per the analgesia ladder. Opiates are frequently required.
Vaccinations – influenza and pneumococcal vaccinations should be given. Live vaccinations are not appropriate for patients with a diagnosis of myeloma.
If the patient has immune paresis (i.e. hypogammaglobulinaemia – low levels of normal immunoglobulins) and has recurrent infections, they may require prophylactic antibiotics +/- IVIG replacement therapy.
Palliative care involvement is often of great value to myeloma patients, and can be introduced concurrently to active treatment, not necessarily reserved for end-of-life.

Useful Links

https://www.myeloma.org/international-myeloma-working-group-imwg-criteria-diagnosis-multiple-myeloma

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