Approaches in Hematology

Hematology Made Easy

Multiple Myeloma

✓ **Multiple Myeloma:** a neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin (abnormal paraprotein) resulting in end organ dysfunction. It is also one of what is called " Paraproteinemias" and " Monoclonal Gammopathies". In Multiple Myeloma, there is usually a single clone of plasma cells, secreting one monoclonal paraprotein either IgG or IgA. It might be preceded by asymptomatic myeloma or MGUS.

✓ **Epidemiology**

- Incidence 3 in 100000, most common plasma cell malignancy
- Increased frequency with age; median age of diagnosis is 68 years; M>F.

✓ **Pathophysiology:** malignant plasma cells secrete monoclonal Ab.

1. 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
   - IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
   - 15-20% produce free light chains or light chains alone found in either:
     - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa: lambda ratio)
     - urine has Bence-Jones protein.
2. <5% are non-secretors.

✓ **Clinical Features and Complications**

1) Bone disease:
   - Pain (usually back), bony tenderness, pathologic fractures.
   - Lytic lesions are classical (skull, spine, proximal long bones, ribs).
   - Increased bone resorption secondary to osteoclast activating factors such as PTHrP.

2) Anemia: weakness, fatigue, pallor, Or secondary to BM suppression
3) Weight loss.
4) infections
   - Usually, S. pneumoniae and Gram-negative bacterial infections
   - Secondary to suppression of normal plasma cell function

5) Hypercalcemia: may present é nausea and vomiting, confusion, constipation, polydipsia. and polydipsia. It is due to increased bone turnover.

6) Renal disease/renal failure: most frequently causes cast nephropathy. Renal failure (the most common cause is from light chain deposition). Usually, the renal damage in MM is tubular. Occasionally there may be glomerular damage with consequent albumin loss (Nephrotic syndrome) with nephrotic range proteinuria.

7) Bleeding:
   - Secondary to thrombocytopenia, may see petechiae, and purpura.
   - Can also be caused by acquired von Willebrand disease.

8) Extramedullary plasmacytoma: it is a soft tissue mass composed of monoclonal plasma cells with purplish color.

9) Hyperviscosity: A triad of visual changes, bleeding, and neurologic impairment results from an increase in blood viscosity by immunoglobulins. It may manifest as headaches, stroke, angina, and MI. It is rare in MM as secondary to increased viscosity caused by IgM protein (more common in Waldenstrom Macroglobulinemia (WM) and Lymphoplasmacytic lymphoma (LPL)).

10) Amyloidosis: occurs due to accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system:
    - Cardiac infiltration: diastolic dysfunction, cardiac arrhythmias, syncope, sudden death
    - GI involvement: malabsorption, beefy large or laterally scalloped tongue (macroglossia)
    - Neurologic involvement: orthostatic hypotension, carpal tunnel syndrome (common in MM)
    - MM-related Amyloidosis may cause Factor X deficiency if fibrils bind Factor X → Bleeding (raccoon eyes)

11) Neurologic disease: muscle weakness, pain, and paresthesias
    - Radiculopathy is caused by a vertebral fracture and extramedullary plasmacytoma.
    - Spinal cord compression (10-20% of patients) and it is a medical emergency.

✓ **Investigations:**

❖ CBC
  - Looking for normocytic anemia, thrombocytopenia, and leukopenia
  - Looking for rouleaux formation on peripheral film

❖ Biochemical labs including Serum Calcium, ESR, ABG & electrolytes, Estimation of Anion Gap, serum Albumin, Creatinine & BUN, Quantification of protein in urine, LDH, and β2-microglobulin.
  - Looking for increased Ca^{2+}, increased ESR, decreased anion gap, increased Cr, albumin, β2-microglobulin, and LDH (as part of staging), and proteinuria (24 h urine collection)

- Monoclonal proteins to detect them do the following:
    - SPEP: (Serum Protein Electrophoresis) demonstrates monoclonal protein spike in serum in 80% (i.e., M protein)
    - UPEP: (Urine protein electrophoresis) demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains).
    - Immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains.
    - Serum free light chain quantification: kappa and lambda light chains, calculated ratio

- BM aspirate and biopsy often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for fluorescence in situ hybridization (FISH) or cytogenetics (prognostic implications).

- skeletal survey (series) (x-rays), MRI if symptoms of cord compression, PET imaging to pick up lytic lesions in asymptomatic MM.
    - To detect the presence of lytic lesions and areas at risk of pathologic fracture
    - Bone scans are not useful since they detect osteoblast activity.

- β2-microglobulin and LDH are poor prognosticators.
- HBsAb, HBsAg, HBc Ab (serology of Hepatitis B virus before treatment)

✓ **Diagnosis:** The current diagnostic criteria for symptomatic multiple myeloma are as follows:

- Clonal bone marrow plasma cells ≥10% or bony or extramedullary plasmacytoma (confirmed by biopsy)

- One or more myeloma-defining events include the following:
    1. Hypercalcemia: Serum calcium level > 1 mg/dL (> 0.25 mmol/L) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
    2. Abnormal kidney function: Serum creatinine > 2 mg/dL (> 177 µmol/L) or creatinine clearance < 40 mL/min
    3. Anemia: Hemoglobin < 10 g/dL, or > 2 g/dL below the lower limit of normal
    4. Bone lesions: One or more osteolytic lesions on skeletal radiography, CT, or PET-CT
    5. Biomarkers of malignancy: Clonal bone marrow plasma cells ≥60% and/or involved/uninvolved serum FLC ratio ≥100 (involved kappa) or < 0.01 (involved lambda) and/or one or more focal ≥5 mm lesions on MRI scans.

✓ **Treatment:** It is a non-curative (often no endpoint)

- Treatment goals
    - Improvement in quality of life (improve anemia, reverse renal failure, prevent fractures)
    - Prevention of progression and complications
    - Increase overall survival.

- Autologous stem cell transplant if <65 years: usually preceded by 4-6 months of cytoreductive therapy: steroid based with novel agents (i.e. Immunomodulatory drugs - IMIDs or proteasome inhibitors - PI).

- Chemotherapy if >70 years or transplant-ineligible: it is pending on patient comorbidities can include a combination of: melphalan, prednisone, cyclophosphamide, PI (i.e., bortezomib), IMIDs (Revlimid), anti-CD38 agents (e.g. daratumumab)

- Supportive management:
  - Bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - Local XRT (radiation) for bone pain, spinal cord compression
  - Kyphoplasty for vertebral fractures to improve pain relief and regain height.
  - Treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe
  - hypercalcemia, prophylactic antibiotics, EPO for anemia, and DVT prophylaxis

- All patients will relapse; the choice of retreatment regimen depends on the duration of remission, organ involvement, patient's comorbidities, and preferences.

✓ **Prognosis:**

- International Staging System (ISS) (β2-microglobulin and albumin) used to stage and estimate prognosis. revised ISS for risk stratification: a combination of original ISS, cytogenetic profile (i.e., p53 mutation associated with poor survival and resistance to chemotherapy), and LDH.

- Median survival based on stage, usually 3-7 years.

✓ **Multiple Myeloma (British guidance):** Diagnosis is based on:

- Monoclonal proteins (usually IgG or IgA) in the serum and urine (Bence Jones proteins).
- Increased plasma cells in the bone marrow
  - The bone marrow aspirate would confirm the diagnosis irrefutably.
  - Bone marrow examination would reveal increased plasma cells (greater than 4% and usually greater than 30%).
  - Bone marrow aspirate --> dark red jelly-like material in the syringe (Plasma cells)
- bone lesions on the skeletal survey

- Diagnostic criteria for multiple myeloma require one major and one minor criterion or three minor criteria in an individual who has signs or symptoms of multiple myeloma.
  - Major criteria
    i. Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
    ii. 30% plasma cells in a bone marrow sample
    iii. Elevated levels of M protein in the blood or urine

- Minor criteria
    i. 10% to 30% plasma cells in a bone marrow sample.
    ii. Minor elevations in the level of M protein in the blood or urine.
    iii. Osteolytic lesions (as demonstrated in imaging studies).
    iv. Low levels of antibodies (not produced by the cancer cells) in the blood.

- Investigations: (NICE 2016)
    1. To confirm the presence of a paraprotein indicating possible myeloma or (MGUS):
        - Serum protein electrophoresis and serum-free light-chain assay
        - If serum protein electrophoresis is abnormal --> use serum immunofixation
        - Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay, or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma.

    2. To confirm a diagnosis of myeloma:
        - Bone marrow aspirate and trephine biopsy.
        - Morphology to determine plasma cell percentage.
        - Flow cytometry to determine plasma cell phenotype.

    3. In a patient presenting with spinal cord compression: the most appropriate initial investigation is -->Urgent MRI of her spine. This should be done before the investigation that is used to confirm myeloma.

- Hypercalcemia in myeloma: primary factor is due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g., IL-1, tumor necrosis factor) released by the myeloma cells. much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels.

- Treatment (NICE 2016)
    I. First-line treatment in previously untreated multiple myeloma (newly diagnosed)
    - Patients who are eligible for high-dose chemotherapy with stem celltransplantation
        - ℛ Bortezomib + Dexamethasone.
        - ℛ Or Bortezomib + Dexamethasone + Thalidomide

    - If high-dose chemotherapy with stem cell transplantation is considered inappropriate
        - ℛ Thalidomide + Alkylating agent + Corticosteroid

    II. People who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation:
        - ℛ Bortezomib (a Proteasome inhibitor) monotherapy.

    III. People who have received two or more prior therapies:
        - ℛ Lenalidomide + Dexamethasone

- Lenalidomide --> immunomodulatory derivatives (structural derivatives of thalidomide)

IV. People with untreated, newly diagnosed, myeloma-induced acute renal disease:
- ℛ Bortezomib + Dexamethasone
- ℛ If bortezomib is unsuitable --> thalidomide + dexamethasone

Note: Do not perform plasma exchange for myeloma-induced acute renal disease.

V. Preventing bone disease, managing non-spinal and spinal bone disease:
- ℛ Bisphosphonates should be given routinely, even in the absence of hypercalcemia. Bisphosphonates reduce bony disease in myeloma, lowering the frequency of pathological fractures, modulate the disease, and have some antitumor activity.
- ℛ Zoledronic acid or Disodium pamidronate, if Zoledronic acid is contraindicated or not tolerated or Sodium clodronate, if Zoledronic acid and Disodium pamidronate are contraindicated, not tolerated, or not suitable.
- ℛ Surgical stabilization followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures.
- ℛ Consider radiotherapy for people who need additional pain relief.

VI. Managing peripheral neuropathy:
- If the patient is on bortezomib --> switch to subcutaneous injections and/or reduce to weekly doses and/or reduce the dose.
- If the patient is on other than bortezomib -->Temporarily stop neuropathy-inducing myeloma treatments if people develop either of the following:
  - Grade 2 neuropathy with pain
  - Grade 3 or 4 neuropathy

VII. Managing fatigue
- ℛ Erythropoietin analogues (adjusted to maintain a steady state of hemoglobin at 110–120 g/liter) to improve fatigue in people with myeloma who have symptomatic anaemia.

VIII. Cord compression secondary to bony involvement of multiple myeloma:
- ℛ I.V Steroids should be commenced immediately.
- ℛ However, the treatment of choice is local radiotherapy.
- ℛ NICE suggests localized radiotherapy should be the first point of call for urgent treatment.
- ℛ Vertebroplasty is typically considered in patients of whom have evidence of metastatic changes in the spine but show no signs of spinal cord compression.

- Surgical decompression: is also considered if imaging suggests any form of spinal instability or structural defects, but often after steroids and radiotherapy has been administered.
- Other treatment options include analgesia, with non-steroidal anti-inflammatory drugs of particular use.

- Prognosis
    - B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Beta-2-microglobulin has been shown to be predictive of risk of progression of disease in myeloma, myelodysplastic syndrome, and chronic myeloid leukemia.

    - In myeloma it is an accurate estimate of total disease load, with guidelines suggesting that a beta-2-microglobulin level of >3.5 mg/L is strongly associated with increased mortality and morbidity.

    - Low levels of albumin are also associated with a poor prognosis.