SUPPORTIVE CARE IN MULTIPLE MYELOMA

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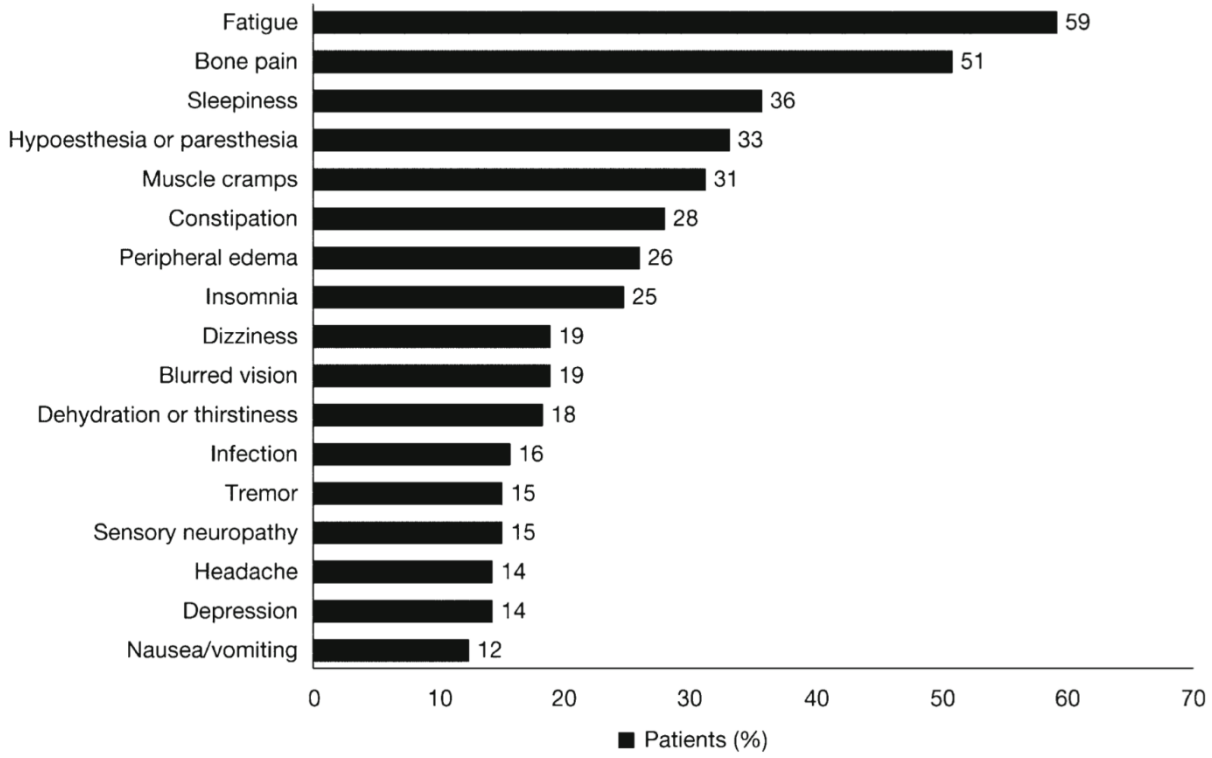
Supportive care: every day challenge

- Myeloma: greatest symptom burden in hematologic malignancies

Fig. 1 Frequently reported multiple myeloma symptoms and adverse events. Collapse of vertebral body, bone fracture, abdominal pain, petechiae/ purpura, gastrointestinal bleeding, upper respiratory tract infection, pneumonia, fever, febrile neutropenia, diarrhea, asthenia or tiredness, anorexia, dyspepsia, motor neuropathy, carpal tunnel syndrome, syncope, states of confusion, mental status changes, cerebrovascular accident, rash, deep-vein thrombosis, hypotension, and renal failure were reported by <10 % of patients



Jordan. Support Care Cancer 2014

Supportive care: every day challenge

- Supportive care impacts
  - Quality of life, daily activities, social functioning, physical activity
  - Treatment tolerance/compliance

  -> Prognosis/survival

- Myeloma = chronic disease -> short and long term vision
  - short term: treatment efficiency against disease
  - long term: treatment tolerance, supportive care, prevention

- Importance of awareness, patient screening

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MM supportive care: Anemia

- 75% at diagnosis

- **Causes:**
  - < medullary involvement
  - < plasmatocytes toxicity on erythroblasts
  - < renal insufficiency
  - < treatments, iron/vitamin deficiency
  - < dilution < hyperproteinemia

MM supportive care: Anemia

- **Management**
  - **Transfusions according to clinical status**

  Warning: at diagnosis with high levels of proteins, always consider dilution and risk of hyperviscosity

  - **ESA** (Erythropoeitin Stimulating Agents)

  -> If persistent Hb < 10g/dl in the context of efficient therapy and without iron/vitamin deficiency

  Types of ESA in Belgium

  * Epoietine alfa (Binocrit® / Eprex®)
  - Darepoetinenalfa (Aranesp®)

  Warning: stop ESA if > 11g/dl, discontinue if ineffective within 6-8 weeks of treatment.

MM supportive care: Bone

- 80% of skeletal related events (SRE) occur within 6 months of diagnosis
- Fractures impact QOL and OS
- Importance to have a look at the imagery
  - Spot bone lesion with imminent risk of fracture
  - Evaluation of importance of vertebral collapse
- Multidisciplinary approach
  - Surgeons: neurosurgeon, orthopedist
  - Radiotherapist: painful lesion, in combination with surgery
  - Pain management
- Basics: vitamine D and calcium supplementation

MM supportive care: Bone

- **Biphosphonates (BP): Zoledronic Acid (ZA) and Pamidronate**
  - Inhibits activity of mature osteoclasts
  - IV administration
  - Facts
    - BP reduce bone pain, SRE and prolong time to first SRE
    - BP in indolent MM reduce SRE but do not impact time to symptomatic disease (Musto, Cancer 2008. D'arena, Leuk Lymphoma 2011)
    - ZA reduces SRE in patients with or without bone lesions at baseline (Morgan, Lancet Oncol 2011)
    - ZA addition to first line treatment improves OS in patient with bone disease at baseline
    - A 2 year BP treatment is recommended based on treatment duration established in studies

MM supportive care: Bone

- **Denosumab**
  - RANKL monoclonal antibody, inhibits osteoclastic precursors
  - SC administration
  - Delay of SRE similar to BP
  - Non-inferior to ZA
  - Rebound effect at end of treatment, caution, shift to another BP

MM supportive care: Bone

Adverse events

- Osteonecrosis of the jaw. *BP = Denosumab*
  - Osteonecrosis of the jaw is a rare but serious adverse event of BP and denotusumab. 1-10% according to studies
  - Additional risk factors: local infection, dental procedure, corticosteroids
  - Imperative stomatologist evaluation before treatment
  - Delay treatment if dental intervention needed, in collaboration with stomatologist (no treatment 90 days before and after dental procedure (IMWG))

- Renal insufficiency. *BP > Denosumab*
  - ZA dose adaptation according to clearance (CBIP/BCFI). Denosumab no dose adaptation

- Hypocalcemia. *Denosumab >>>>> BP*

MM supportive care: Bone

- Reimbursement in Belgium
  - ZA = Zometa® : MM stage III, CI if clearance < 30
  - Denosumab = Xgeva® : MM with bone lesion and renal clearance < 30
- Cost: Denosumab >>>>>>> ZA
- In practice
  - Treatment during two years for patient with bone lesions
  - Consider denosumab for patient with clearance < 30
  - Restart BP when relapse

MM supportive care: Hypercalcemia

- Importance of considering corrected calcemia

- **Track complications**
  - Cardiac: QT, contractility, arythmia
  - Neurological: confusion, urinary retention, coma
  - GI: constipation, nausea, vomitting
  - Renal: polyuria, renal insufficiency

- **Management**
  - IV hydration
  - Corticosteroids
  - Calcitonin (temporary effect)
  - Bisphosphonates
  - Hemodialysis
  - Furosemide NOT recommended

MM supportive care: Renal disease

- **Emergency at diagnosis**
  - IV hydration with follow-up of fluid balance
  - Dialysis
  - Controversial: urine alcalisation, dialysis with light chain membrane
  - Anti-MM therapy: corticosteroids, bortezomib

- Evaluation of proteinuria for underlying mechanism
  - Globulin versus Albuminuria (amyloïdosis)

- Collaboration with nephrologist

- **All MM patients have renal frailty irrespective of creatinin levels -> renal preservation for ALL patients**
  - Oral hydration
  - CI to NSAIDs
  - CI to contrasts agents

MM supportive care: Infections

- 7 times more bacterial infections and 10 times more viral infections compared to general population

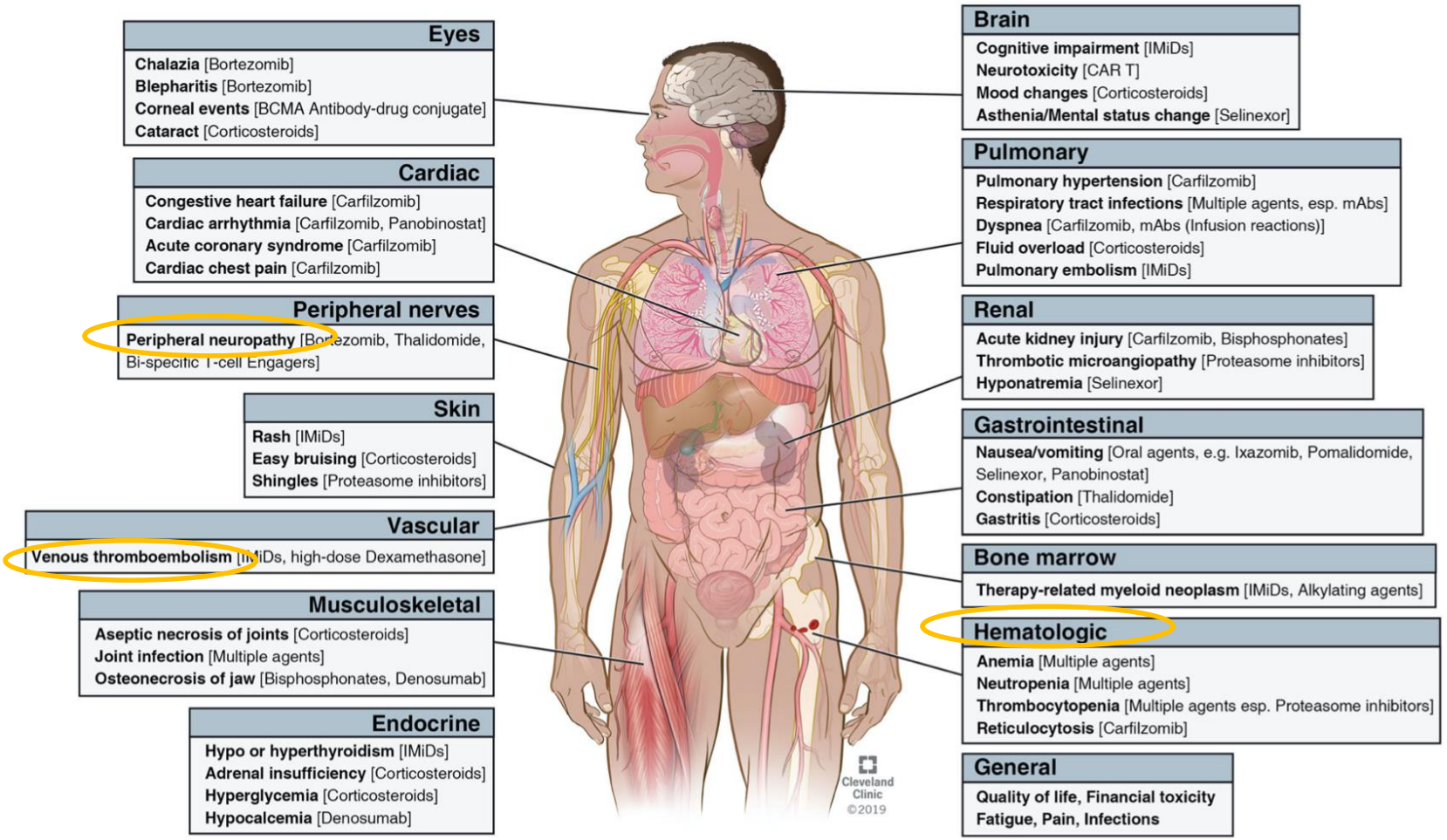
- Recommended **vaccination** for all MM patient (EMN 2021)
  - Influenza
  - Pneumococci: Apexxnar
  - Haemophilus influenzae

- **Prophylaxis** under treatment
  - Aciclovir 400mg 2 times a day
  - Eusaprim 3 times a week

MM supportive care: Infections

- **Immunoglobulins**
  - Indication: low immunoglobulin levels AND life-threatning infection and/or recurrent infections treated with antibiotics
  - Seasonal treatment, rechallenge indication every fall/winter
  - In practice:
    - IV (Privigen or Multigam): 0,4g/kg every 4 weeks. Adjust according to Ig levels before next administration (0,5g/kg and/or every 3 weeks)
    - SC (Hizentra): if iv well tolerated, monthly dose divided by 4, can be self administered at home

Treatments' supportive care



Chakraborty. AJH 2020

Treatments' supportive care

- Always consider dose adjustments in case of
  - Renal insufficiency
  - Adverse events such as cytopenias, polyneuropathy, toxidermia, GI intolerance…

→ Clear instructions in drugs compendium according to treatment protocols cfr CBIP/BCFI website. When to interrupt, stop, dose level adjustments etc

Treatments' supportive care

- Always consider dose adjustments
  - According to patient's frailty especially in the elderly

APPENDIX 3. Therapy doses adaptation regarding risk factors in elderly patients. Adapted from Palumbo, Blood Rev 2013.[105]

	Risk factors	point(s)
Age	≥75 years	1
co-morbidities	cardiac, pulmonary, hepatic, renal, marrow dysfunction	1
Frailty	weakness, poor endurance, weight loss, low physical activity, slow gait speed	1
Disability		1

Risk factors	dose level adaptation
0	**0**
≥1	**-1**
≥1 and previous grade 3-4 non-hematologic toxicity	**-2**

Vekemans. BJH 2020

Treatments' supportive care: PNP

- Polyneuropathy
  - Present at diagnosis?
  - Concurrent amyloïdosis? B12 deficiency? Diabetes?
  - **Definition**
    - Grade 1 : asymptomatic clinical or diagnostic observations or mild paraesthesia.
    - Grade 2 : moderate symptoms that limit instrumental ADL like preparing meals, shopping, using a telephone and managing money.
    - Grade 3 : severe symptoms that limit self-care ADL like bathing, dressing and undressing, feeding oneself, using the toilet and not being bed ridden.
    - Grade 4 : associated with life threatening consequences

Mohty, Hematologica 2010.

Treatments' supportive care: PNP

- Polyneuropathy
  - Drugs: bortezomib, thalidomide

	Bortezomib	Thalidomide
Incidence	➢ < 40% ❖ Grade I-II: 30% ❖ Grade III-IV: < 10% ➢ Plateau around C5	➢ 70% in certain trials (12 months trt) ❖ Grade I-II: 50% ❖ Grade III-IV: 20% ➢ Risks increases with exposure
Type	Mainly sensory, motor rare. Painful (cold exposure). 10% dysautonomy	Mainly sensory, often motor
Management	Dose adjustments, weekly instead of biweekly	Limits dose and duration of treatment
Recovery	Reversible > 50% of patients if dose adjustment. Median time to recovery 6-8 weeks	Often irreversible

Mohty, Hematologica 2010.

Treatments' supportive care: PNP

- Management
  - **Dose reductions** cfr CBIP/BCFI
  - **Symptoms/Pain relief**
    - Amitriptyline (Redomex)
    - Pregabaline (Lyrica)
    - Tramadol
  - **Physiotherapy**: improve proprioception (hands and feet), physical exercise

Mohty, Hematologica 2010.

Treatments' supportive care: VTE

- 10% of patients
- Higher risk during the first 6 months of NDMM. Lower risk at relapse
- Considerations
  - Risk related to the patient
  - Risk related to disease
  - Risk related to treatment (IMiDs, high dose dexamethasone)

  -> Scores

Treatments' supportive care: VTE

Table 1. International Myeloma Working Group, European Myeloma Network, and National Comprehensive Cancer Network risk stratification algorithm and choice of thromboprophylaxis in patients with multiple myeloma. IMiD: immunomodulatory agent, MM: multiple myeloma, VTE: venous thromboembolism.

Algorithm for MM Patient Risk Stratification		
Patient-Related Risk Factors ***ASSIGN 1 Point for Each of the below:***	**Disease-Related Risk Factors:** ***Assign 1 Point for Each of the below:***	**Treatment-Related Risk Factors:** ***Assign Points as Seen below:***
Body mass index >25, Age >75, Personal or family history of VTE, Central venous catheter, Acute infection or Hospitalization, Blood clotting disorders or Thrombophilia, Immobility with performance status of >1, Comorbidities (liver, renal impairment, chronic obstructive pulmonary disorder, diabetes mellitus, chronic inflammatory bowel disease), Race (Caucasian is a risk factor)	• Diagnosis of multiple myeloma • Evidence of hyperviscosity	• IMiD in combination with low-dose dexamethasone (<480 mg/month) *(1 point)* • IMiD plus high-dose dexamethasone (>480 mg/month) or doxorubicin or multiagent chemotherapy (*2 points)* • IMiD alone (*1 point)* • Erythropoietin use (*1 point)*
Risk stratification and recommended thromboprophylaxis: 0 points: Low risk ***None*** 1 point: Intermediate risk ***Aspirin at 100 mg*** >1 points: High risk ***Low molecular weight heparin at prophylactic dose or therapeutic dose of warfarin***		

Foutiou, Cancers 2020

Treatments' supportive care: VTE

- **Which kind of prophylaxis**
  - Palombo 2011: no difference Asp/LMWH/warfarin except elderly patients where LMWH > warfarin
  - Rationale for use of aspirin in low risk patients:
    - Enhanced platelet activation induced by IMiDs
    - Altered platelet function in patients with MM
  - DOACs considered but not yet reimbursed
  - For the first 4-6 months or as long as the risk remains high

Treatments' supportive care: VTE

- **Problems with prophylaxis** : in real life and studies, VTE still a concern
  - Prophylaxis not always (correctly) administered
  - Need of a better risk stratification
    - only 55% of patients who develop thrombosis were defined as high risk
    - « stronger » prophylaxis in very high risk patient

Treatments' supportive care

- GI:
  - loperamide
  - Questran

- Hypertension/fluid overload (Carfilzomib, corticosteroids)
  - Low salt regimen
  - Tension control
  - Cardiac evaluation

  See 2022 ESC guidelines on cardio-onology (p 2468) for specific cardiac risk stratification in multiple myelome and management according to risk.

  App available.

Take home message

- Improving symptom burden from disease and treatment improves compliance, QOL and OS

- Multiple disease + Multiple treatments = Multiple considerations
  - Multidisciplinnary collaboration
  - Supportive treatment = Supportive team (doctor, oncology nurse, physiotherapist, psychologist, pain clinic)

Thank you