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Toxicity Management

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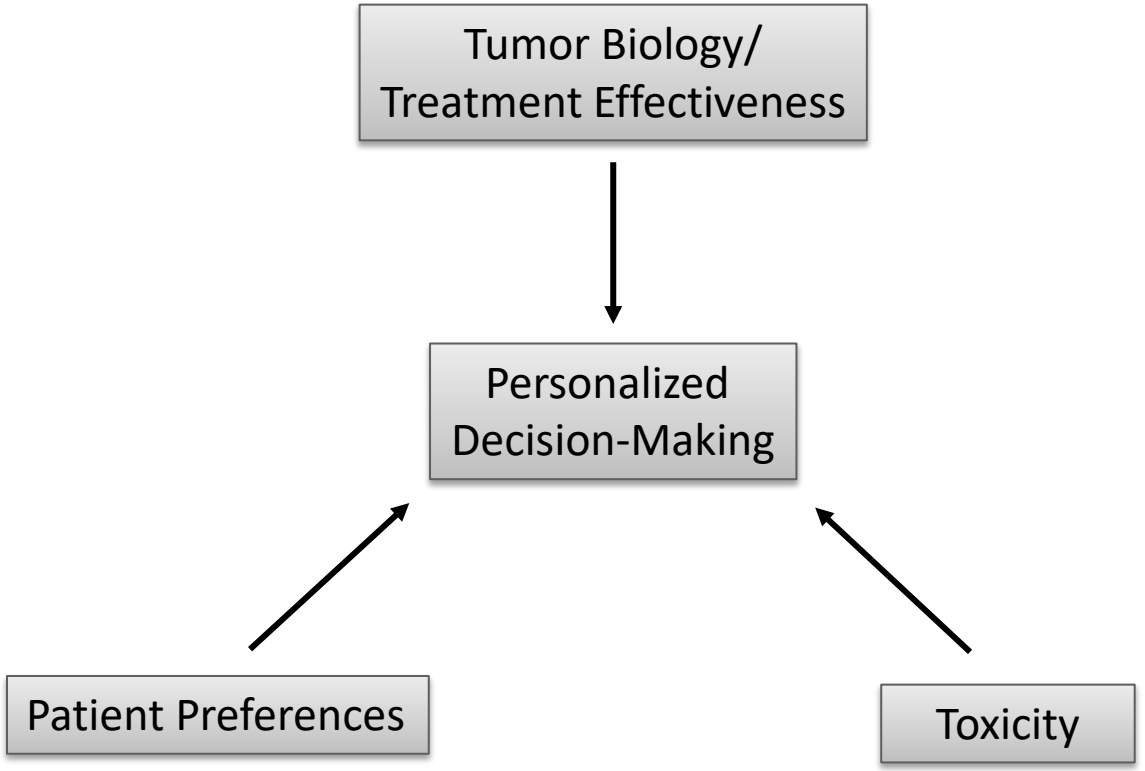
MASSACHUSETTS
GENERAL HOSPITAL

CANCER CENTER

Clinical Management

Selecting a Specific Regimen:

- Patient factors
  - Age
  - Frailty
  - Other medical problems
  - Prior experience with drug/drug class
- Disease factors
  - Molecular profile
  - Pattern of organ involvement
  - Other risk factors
- Medication factors
  - Specific toxicities
  - Out-of-pocket costs



Is Less More?

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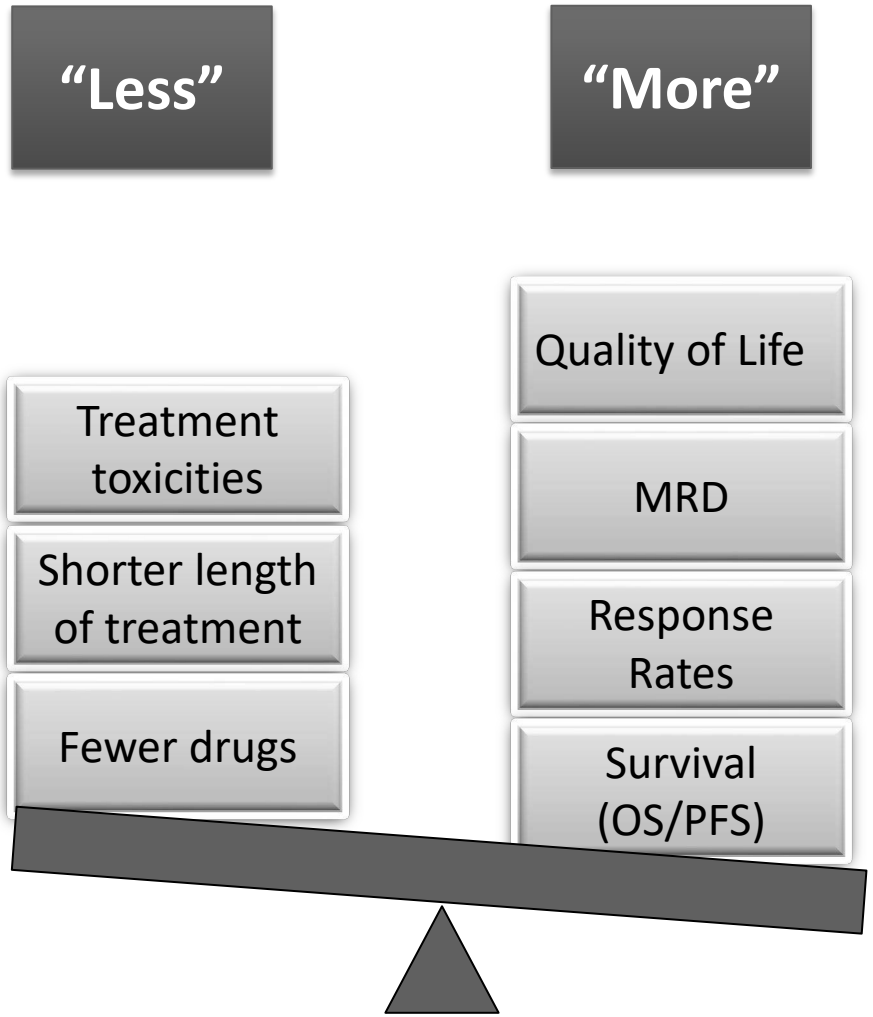
- Yes, if toxicity of regimen is greater and negates the benefit of improved disease control
- No, continuous therapy associated with better outcomes when toxicity is comparable
- Aim for maximizing tolerability



Clinical Management

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Goals of Therapy

- Improve organ function
- Relieve pain and disease-related symptoms
- Maintain activity and function
- Disease Control: Deeper responses improve outcomes in transplant-eligible and transplant-ineligible patients
  - Minimal residual disease (MRD) negativity is prognostic for PFS & OS
  - MRD can be achieved in patients not undergoing ASCT
- **Balance quality of life and achieving deep response**

Clinical Management

Comorbidities in MM

- Incidence of comorbidities increase with age
- Comorbidity is associated with increased mortality in both younger and elderly patients with MM
- Comorbidities increase vulnerability to therapy toxicities

- **Managing comorbidities in MM requires attention to the individual patient**
- **Select therapy wisely, avoid drugs that worsen specific comorbidities**
- **Upfront dose modifications**
- **Close follow-up!**

Gregersen, H et al. *Cancer Med* 2017;6:1807-1816

Case

Mr. Jones is a 63M who presents with back pain. Imaging reveals a new compression fracture at T11 and multiple additional lytic lesions. He has a mild anemia, no hypercalcemia and preserved renal function. SPEP significant for 3.2 g/dL IgG kappa M-protein, kappa free light chain 732 mg/L. Bone marrow biopsy shows 40% plasma cells with standard-risk cytogenetics.

Mr. Jones is started on the following regimen for the treatment of newly diagnosed MM:

Lenalidomide 25 mg po Days 1-14

Bortezomib 1.3 mg/m2 sc Days 1, 4, 8, 11

Dexamethasone 20 mg po Days 1, 2, 4, 5, 8, 9, 11, 12

After one cycle he returns to your office in follow-up. His pain is well-controlled but he complains of insomnia.

Why Does Sleep Matter?

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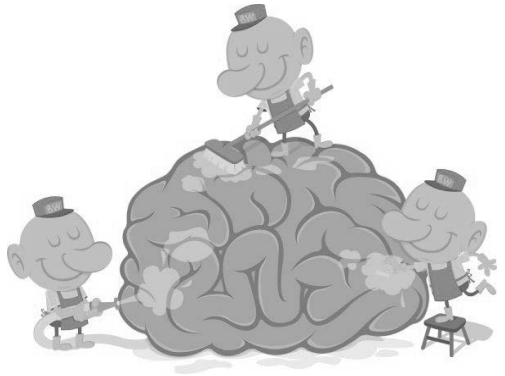
- Adequate sleep quality plays a central role in maintaining individuals' physiological and mental health
- Poor sleep quality and duration has been linked with a range of outcomes such as increased risk of infection, cardiovascular disease, diabetes, cognitive impairment, metabolic dysfunction, and mood-related disorders such as depression and anxiety
- Disturbed mood has been found to be associated with fatigue severity, which might be further exacerbated by MM medications such as steroids



Sleep and MM

- Pain
- Steroids
- Peripheral neuropathy
- Psychological distress

Steroids

The MM treatment course is distinguished by continuous, high-dose steroid usage

This prolonged exposure makes MM patients particularly vulnerable to:

- Insomnia
- Mood alteration
- Change in body composition - loss of lean muscle, gain of visceral adipose tissue
- Increased appetite
- Weight gain
- Hyperglycemia
- Hyperlipidemia

All of these issues are modifiable or potentially preventable side effects that can affect long-term survival and QOL

Steroids – Dose Reductions

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Rd-R v Rd - 9 x 28-day cycles

- Rd-R
  - Lenalidomide 25 mg Days 1-21
  - Dexamethasone 20 mg Days 1, 8, 15, 22

  ➢ Lenalidomide maintenance 10 mg Days 1-21 days until disease progression

- Continuous Rd – until disease progression
  - Lenalidomide 25 mg Days 1-21
  - Dexamethasone 20 mg Days 1, 8, 15, 22

- EFS 10.4 vs 6.9 months (HR 0.70, p=0.02)
- OS at 3 years 74% v 63% (HR=0.73, p=0.06)
- No differences in OR or PFS
- Fewer dose reductions in Rd-R

Larocca et al. *Blood.* Jun 3;137(22):3027-3036.

Steroids - Clinical Management

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- Keep communication open with patient and caregivers
  - **Discuss symptoms such as insomnia, mood swings, hyperglycemia**
  - **Discuss timing of taking steroids – AM preferred**
- Dose-adjust, as necessary
- Consider upfront dose modifications for older/frail patients

Case Continued

Mr. Jones returns to clinic to initiate Cycle 4

On review of systems:

- He reports worsening numbness of the soles of his feet
- He describes the sensation as feeling as though he is walking on sand

Peripheral Neuropathy

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- Route of administration – IV vs SC
- Dose reduce!
- Treatments:
  - Anti-depressants (TCAs, SNRIs) and anti-convulsants (gabapentin, pregabalin) are first-line
  - These drugs can be used in combination with opioids
  - As with opioids, response to analgesics may vary according to the etiology of neuropathic pain and the individual patient: failure to control pain with one agent in a particular class does not mean the entire class of medications will not work
  - Patient education should emphasize the trial and error nature of the treatment so patients do not get discouraged
  - Doses should be increased until the analgesic effect is achieved, adverse effects become unmanageable, or the conventional maximum dose is reached
  - Drug selection may be influenced by other symptoms and comorbidities. For example, a sedating drug may be useful in a patient in whom insomnia is a problem
  - Consider cannabinoids and medical marijuana

https://www.nccn.org/professionals/physician_gls/pdf/pain_core.pdf

Case Continued

Mr. Jones returns to clinic at Day 100 post-autologous stem cell transplant

He has recovered well from this treatment and is prepared to begin lenalidomide maintenance today

On review of symptoms, he reports:

- Has trouble “shutting off mind”, worries about disease recurrence
- Reports fears of not being able to see his youngest daughter get married
- Worries about his financial welfare and being able to continue to work for a few more years to save a little more money for his wife

Psychological/Emotional Toxicity

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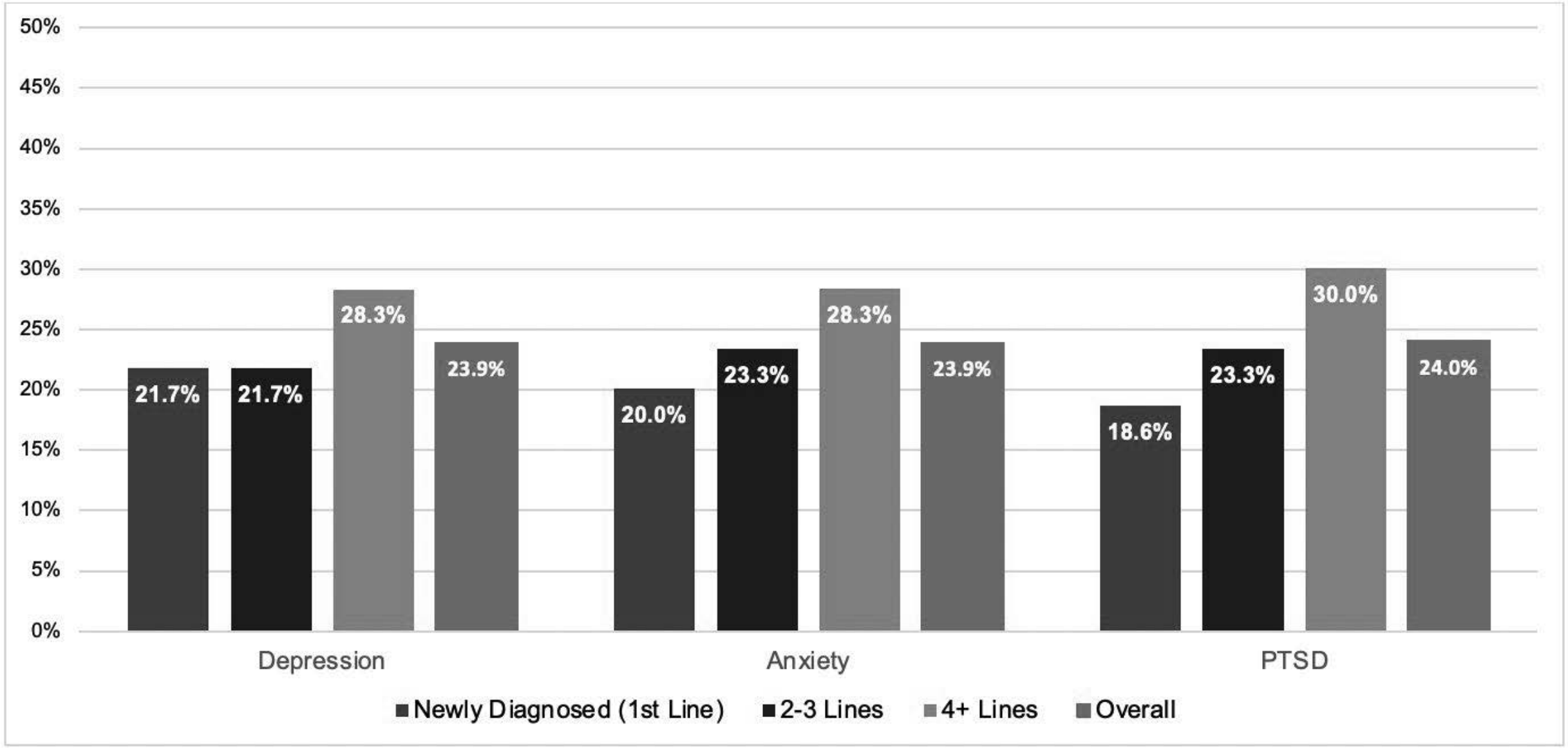

O'Donnell et al. IMW Abstract 2021

Antidotes to Stress

- Mind body therapies- meditation, yoga, tai chi, prayer, acupuncture/acupressure
- Exercise – aerobic and strength training
- Balanced nutrition
- Positive emotions, humor, gratitude
- Support – relationships / social connectedness
- Restorative sleep

Social Support for Cancer Patients

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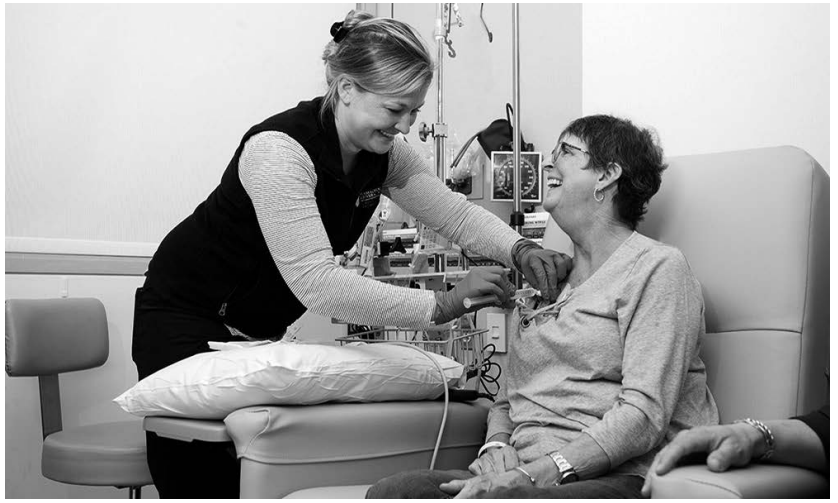
Cancer itself can be an isolating experience physically and emotionally

- Long treatment sessions
- Being immunocompromised during therapy may require limiting exposure to the outside world
- Emotional isolation can occur due to lack of peer group with similar experience, a sense of vulnerability



When is Social Support Needed?

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Through all phases of cancer

- From work up
- Diagnosis
- Active treatment
- Rehabilitation
- Survivorship
- End of life

Case Continued

Mr. Jones returns to clinic for follow-up

- He remains in a CR after induction therapy with RVD and autologous stem cell transplant.
- He has been on lenalidomide maintenance for 2 years
- On review of symptoms:
  - He reports post-prandial diarrhea
  - Episodes are accompanied by fecal urgency

Lenalidomide-Related Diarrhea

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- Commonly observed during long-term maintenance therapy on lenalidomide
- Bile acid malabsorption (BAM)
  - Excess bile acids are not absorbed in the small intestine and enter the large intestine causing symptoms of loose, watery stool, bloating, and inability to control bowel movements
- Lactose intolerance
- Recommend a stepwise approach:
  - First, try dietary modifications along with over-the-counter medications
  - If these changes are not enough, prescription medications may be necessary

Lenalidomide-Related Diarrhea

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Dietary Modifications:

Avoid/Limit:

• Fatty food (fried food, high-fat meals, oil-based salad dressing)

• Dairy products (milk, cheese, yogurt, ice-cream); Instead, try non-lactose or non-dairy/plant-based alternatives (soy, coconut, almond, oat milk)

BRAT diet:
B – Banana
R – Rice
A – Apple sauce
T – Toast

• This bland “binding” food diet can decrease episodes of medication-induced diarrhea

Lenalidomide-Related Diarrhea

Over-the-counter medications/supportive agents:

Use to treat acute episodes:

• **Loperamide (Imodium A-D®)** – can help control acute episodes of diarrhea – take 4 mg (2 pills) by mouth initially, followed by 2 mg after each loose stool; can be safely taken up to 16 mg/day (8 pills)

May use as prevention:

• **Psyllium (Metamucil®)** – a bulk fiber can help make bowel movements more formed and less fluid

• **Probiotics/Lactobacillus acidophilus** – have shown some benefit

Lenalidomide-Related Diarrhea

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Prescription medications:

Cholestyramine resin (Questran®) – available in powder form, take 4 g (1 packet) by mouth once daily initially, may need to increase to 2-3 times a day

• **Colestipol (Colestid®)** – available in tablet form, take 2 g (2 pills) by mouth once or twice daily, may need to increase to 2-3 times a day

• These medications are known as bile acid sequestrants and are commonly used to lower cholesterol, but they been shown to be effective for BAM as well

• Caution – some medications can bind to these agents and decrease absorption. Your pharmacist can help you identify if any medications need to be taken at a separate time.

Clinical Management

Supportive care

- Proteasome inhibitors/anti-CD38 antibodies: shingles prophylaxis
- IMiDs: blood clot prophylaxis
- Corticosteroids: consider GI prophylaxis
- Evidence of bone disease: zoledronic acid or denosumab (preferred if renal dysfunction)

  *pain control / interventions such as vertebroplasty / kyphoplasty
- Infection prophylaxis:
  - Vaccines (pneumococcal, yearly influenza, shingles, COVID)
  - Antibiotics are actively being studied
  - IVIG if recurrent life-threatening infections or IgG<400
- Social Work
- Palliative Care
- Physical Therapy & Rehabilitative Medicine

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Clinical Management of Toxicity

- Balance of achieving a deep response with quality of life
  - Dose adjust
- Consider all forms of toxicity:
  - Medication
  - Psychosocial
  - Financial
- Communication
  - Understand patient values and priorities
  - Ask patients and caregivers about symptoms

Thank you

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