Consensus Recommendations for the Clinical Management of Patients With Multiple Myeloma Treated With Selinexor

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Introduction

Despite being an incurable disease, life expectancy after diagnosis of multiple myeloma (MM) has more than doubled owing to novel treatments and autologous stem cell transplant in eligible patients.[1,2] There are now over 10 United States Food and Drug Administration (FDA)-approved agents for the treatment of MM, and the standard of care has been to leverage their mechanism of action by using them in combinations with corticosteroids such as dexamethasone. The key 3 classes of novel agents are proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. Although highly effective agents exist in these 3 classes, nearly all patients will become refractory to them at some point during the course of their disease. Once patients become "triple-class" refractory, very few effective anti-myeloma options remain. Selinexor, a first-in-class oral nuclear transport inhibitor, targets clonal plasma cells by blocking tumor suppressor proteins from being exported from the nucleus; selinexor forces nuclear restoration and reactivation of tumor suppressor proteins, leading to selective induction of apoptosis of cancer cells.[3]

Selinexor was approved in 2019 by the FDA in combination with dexamethasone for patients with relapsed MM previously treated with at least 4 prior therapies and refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. This indication received accelerated approval based on the response rate from the STORM trial (KCP-330-012; NCT02336815).[4] This study included 122 patients who had previously been treated with 3 or more regimens including an alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy. The overall response rate was 25.3% in the subset of 83 patients who were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.

In the 202 patients treated in the STORM trial, the most common adverse reactions (incidence 20% or greater) were thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory infections (Table 1). Treatment discontinuation owing to adverse events occurred in 27% of patients. Dose reductions occurred in 53% of patients, and 65% of patients required a dose delay. The most frequent causes of permanent discontinuation owing to adverse reactions were fatigue, nausea, and thrombocytopenia. Fatal adverse reactions were seen in 9% of patients.[4]

There have been several studies employing selinexor both as a single agent and in combination with other drugs. With greater use of the drug, increased confidence and comfort in its use has resulted in better prevention and efficient management of adverse events. Several general principles or "tips" are summarized here, followed by a practical guide to managing the most common adverse events. It is also important to recognize that these patients in the STORM trial were heavily pretreated and were often older and frail, with disease-related and -unrelated comorbidities. Patients receiving selinexor

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often have limited bone marrow reserve owing to multiple prior therapies received. As a result, even lower grade toxicities can be impactful and will require prompt intervention by the health care provider and/or patient to prevent further worsening of consequences. Identifying the symptoms related to the drug and early intervention are the key strategies to effectively deliver the drug to obtain the anti-myeloma response.

The Practical Administration of Selinexor

The prescribing information for selinexor is the gold standard when administering the agent to patients.[5] However, in addition to that guidance, our goal is to provide practical strategies that will enable a facilitated administration of the drug to maximize the efficacy of the agent and to effectively address the predictable toxicities known to be caused by this agent. Listed below are 5 key strategies found to be helpful with selinexor administration based on this consensus panel's cumulative experiences, and guidance from the manufacturer.

Patient Education

Ensuring there is clear and open communication with the patient and their caregivers is particularly important when administering selinexor. Patients should be informed about the high likelihood of symptoms such anorexia, nausea, and fatigue and encouraged to monitor and report early signs and symptoms. In our clinical practices, we ask patients to have a diary recording their symptoms. Indeed, patients and caregivers will be critical participants in the process in routinely checking their weight and vital signs, adequately hydrating, and monitoring for other common side effects of the treatment as outlined below. Setting expectations for possible dose delays and reductions is also helpful to ensure that patients can continue therapy safely. We communicate to our patients that approximately 50% of patients on the STORM clinical trial required a dose reduction.

Setting Up Expectations and Close Monitoring of Patients is Required - Especially in the First Cycle

We have found that during the consenting and education process, it is helpful to tell patients that most patients who respond do so in the first month. However, the most challenging time to manage side effects of this agent is also during the first month. Fortunately, because the drug has a short half-life of 6 to 8 hours (although the half-life of pharmacodynamic changes with respect to XPO mRNA expression can be up to 48 hours), patients are informed that if aggressive supportive care is not adequate for adverse event management, dose holds followed by reduction are very effective.

In most of our centers, we schedule a clinic visit with the patient and administer hydration at least weekly (and those with baseline cytopenias, at least twice weekly, provider assessment weekly), assess for toxicities, and intervene before they worsened. Communication is always critical in providing optimal oncology care, but is most crucial during the first cycle of selinexor therapy. We learned quickly, for example, that we could prevent more severe grades of fatigue and anorexia by frequently communicating with the patient and often their caregiver, and addressing emergent adverse side effects. As patients become accustomed to selinexor, the agent becomes better tolerated.

Nursing Engagement

In conjunction with the above strategies, close communication and engagement with the nurses enhanced selinexor outcomes. Indeed, a nursing education program established during the clinical trials demonstrated a reduction in the incidence and severity of adverse events. In order to model best-practices within the clinical trials setting, effective nursing management requires that the nurses within each oncology practice be well-educated in the administration and management of side effects and toxicities associated with selinexor. A multidisciplinary approach that includes physicians, advanced practice providers, nurses, trained nurse navigators, pharmacists, and nutritionists is most helpful in successfully caring for patients with MM in need of symptom management.[6]

Supportive Care More Prominent Than With Most Oral Agents

Although selinexor is an oral agent, it requires significant supportive care — especially early on in therapy — which is unlike the majority of oral agents used to treat MM. Supportive care is centered around mild to moderate cytopenias, mild to moderate nausea, anorexia, some gastrointestinal toxicity, and fatigue.[4] A proactive approach in supporting patients on selinexor is critical as adverse effects can intensify in a short period of time when compared with other agents and then become more difficult to manage. This will require a more intensive approach to monitoring adverse events and follow-up of patients.

Prophylaxis of Nausea From the Start

Prophylactic prevention of nausea and anorexia is more successful in controlling these symptoms than starting the antiemetic after the symptoms begin. As per the label, all patients should be started on a 5-HT3 antagonist such as ondansetron. In addition, in our experience, adding low-dose daily olanzapine and/or neurokinin 1 (NK_1) receptor antagonists significantly reduced the incidence and severity of nausea. NK_1 receptor is a G protein-coupled receptor located in the central and peripheral nervous system. Because it is believed that nausea is triggered centrally and selinexor does penetrate the blood brain barrier, an NK_1 receptor antagonist such as rolapitant or aprepitant might be very potent.[7]

Olanzapine, among others, is an atypical antipsychotic primarily and has no FDA indication for nausea. Nevertheless, in randomized trials, it has been shown to significantly reduce chemotherapy-induced nausea.[8-10] With time, olanzapine could be tapered or discontinued, but in our practice, it was particularly helpful in the first 1 to 2 cycles. Efforts should be made to ensure that supportive care anti-emetics are available to the patient concurrent with the start of selinexor-based therapies.

Managing Adverse Events

We highlight the most common and most severe side effects of selinexor, namely gastrointestinal toxicity, thrombocytopenia, and fatigue, and share our approach to treat those side effects. Dose reductions based on toxicity can be a valuable strategy to maintain patients on treatment, especially when few treatment options are

Table 1 Most Commonly Reported AEs in Response to Selinexor and Clinical Response by Dose Reduction or Discontinuation

Preferred Term	STORM Part 2 (N = 123), %				
	All Grades	Grade 3	Grade 4	AE Leading to Dose Modification	AE Leading to Discontinuation
Hematologic					
Thrombocytopenia	73	27	32	47	3
Concurrent bleeding AE	18	4	0	NA	NA
Neutropenia	38	19	3	16	0
Febrile neutropenia	2	2	0	NA	NA
Anemia	66	42	1	23	2
Leukopenia	31	12	0	NA	NA
Lymphopenia	16	8	3	NA	NA
Non-hematologic					
Fatigue	63	20	NA	29	4
Nausea	70	10	NA	19	6
Weight decrease	49	0	NA	12	4
Hyponatremia	35	20	1	6	0
Decreased appetite	54	4	0	8	2
Vomiting	37	3	0	5	2
Diarrhea	42	7	0	NA	NA

Abbreviations: AE = adverse event; NA = not applicable; STORM = Selinexor Treatment of Refractory Myeloma.

available. The recommended starting dose of selinexor is 80 mg days 1 and 3 of each week (160 mg total per week). Of note, the product insert should be referenced for all potential side effects patients experience, and dose reductions based on toxicity grade (see Table 2 for a summary).

Gastrointestinal Toxicity

Some of the most common, non-hematologic adverse effects of selinexor in the STORM clinical trial were nausea, vomiting, decreased appetite, decreased weight, and diarrhea. These might be mitigated with the following strategies:

1. Prophylactic anti-nausea agents with an 5-HT3 antagonist (ondansetron).
2. NK_1 receptor antagonist such as rolapitant or aprepitant might be very potent. However, they appear to work best when used in conjunction with serotonin receptor antagonists and dexamethasone.[11] NK_1 receptor antagonists include the oral agent aprepitant, its parenteral version fosaprepitant, netupitant, and rolapitant.
3. Low-dose olanzapine should be considered. Patients should be monitored because olanzapine can cause extrapyramidal effects and increases the risk for serotonin syndrome. Regular electrocardiograms should be performed because olanzapine can prolong QTc interval.
4. Maintain hydration of at least 2 liters daily, preferably not only water, but include salt-containing drinks such as sport drinks or Pedialyte to minimize risk of hyponatremia.
5. Check daily weight and intervene with patient education on high-calorie snacks if weight is dropping (Table 3).
6. If appetite and weight are not maintained with regular foods and additional food snacks, supplements may be added, such as Boost or Ensure.
7. Consider a nutritional consult if available in all patients or at least in patients who are unable to maintain their weight.
8. Consider scheduling intravenous fluids on a regular schedule when starting selinexor. Simply providing 500 mL of fluids weekly or twice weekly allowed for enhanced hydration and facilitated a conversation with the nursing team about side effects, the importance of oral hydration, and nutritional status. Advise patients to consume small, frequent meals or snacks and to avoid large meals or fried and greasy foods.[12]
9. Appetite stimulants, namely megestrol acetate, are not routinely recommended but can be considered.
10. Dronabinol is available with prescription for 2 FDA indications: (1) AIDS-related cachexia and (2) chemotherapy-related nausea. In selected patients with cachexia and nausea, dronabinol can be given at a dose of 2.5 mg orally twice a day for patients above 65 years, and 5 mg orally twice a day for patients below 65 years.[13]

Thrombocytopenia

Thrombocytopenia is the most common hematologic adverse event with selinexor and is often exacerbated by lower starting platelet counts in heavily pretreated patients. Of note, the rates of thrombocytopenia are actually higher in patients with MM relative to patients with lymphoma and solid tumors, likely reflecting the increased marrow replacement by cancer in MM.

1. Monitoring of platelet counts is important, and a general recommendation for frequency is as follows:
   a. Check platelet count weekly
   b. If starting platelet count 50,000/μL, blood check twice weekly

Table 2 Summary of the AEs: Practical Supportive Care and Dosing Recommendations from the Consensus Panel

Symptom	Prophylaxis	Treatment
Fatigue	Check for underlying modifiable factors for fatigue (depression, dehydration, anemia, drugs, hypothyroidism, adrenal insufficiency) Encourage exercise, hydration and rest	**Grade 1:** Maintain dose Rule out other causes of fatigue (dehydration and anemia) Consider transfusing for hemoglobin < 8 g/dL Institute supportive care medications per institutional guidelines and NCCN CPGO **Grade 2:** Lasting > 7 days or Grade 3: Rule out other causes of fatigue (dehydration and anemia) If anemic, consider transfusing for hemoglobin < 8 g/dL Institute supportive care medications per institutional guidelines and NCCN CPGO Interrupt selinexor dosing until resolved to Grade 1 or baseline For first occurrence, restart selinexor at current dose For ≥ 2nd occurrence, reduce selinexor by 1 dose level when resuming selinexor
Anorexia	Schedule weekly office visits to track body weight.	**Grade 1 or 2:** Maintain dose Rule out other causes Consider a repeat nutritional consultation and nutritional supplements (eg, Ensure, Boost, etc.) Institute supportive care medications per institutional guidelines and NCCN CPGO **Grade ≥ 2** weight loss or **Grade ≥ 3** anorexia: Rule out other causes Consider a repeat nutritional consultation and nutritional supplements (e.g., Ensure, Boost, etc.) Institute supportive care medications per institutional guidelines and NCCN CPGO Interrupt dosing with selinexor until improves to Grade 1 or baseline and weight stabilizes Reduce selinexor by 1 dose level when resuming treatment
Nausea and vomiting	Recommend 5-HT3 antagonist to be taken before the first dose, and 2-3× daily as needed for nausea.	**Grade 1 or 2** (If intolerable or persistent Grade 2 not responsive to supportive care, follow guidelines for Grade 3 below): Maintain dose. Rule out other causes of nausea. Implement additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists using institutional guidelines and NCCN CPGO. Add olanzapine daily for 1-2 months **Grade 3:** Rule out other causes of nausea and add NK_1R antagonist and continue as above. Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline and restart selinexor at 1 dose level lower
Hyponatremia	Maintain fluid intake and encourage salty foods, snacks	**Grade 1** with sodium levels < normal to 130 mmol/L: Maintain dose Rule out other causes including drug (eg, diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Consider paraproteinemia as a cause of hyponatremia in heavily pretreated patients with multiple myeloma. Treat hyponatremia per institutional guidelines including dietary review **Grade 2:** Consider addition of salt tablets to patient's diet, salty foods **Grade 3** with sodium levels 120 to < 130 mmol/L without symptoms: Correct for hyperglycemia as outlined under Grade 1 Treat hyponatremia per institutional guidelines If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that intravenous saline and/or salt tablets (1-3 times daily) are provided If Grade 3 is persistent or worsens or does not respond to treatment, hold selinexor until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level: Grade 3 with sodium levels 120 to < 130 mmol/L with symptoms or Grade 4 (<120 mmol/L): Correct for hyperglycemia as outlined under Grade 1. Delay/hold selinexor until resolved to Grade 1 or baseline then reduce selinexor dose by 1 level
Diarrhea	Maintain oral hydration with at least 8-8oz glasses of fluid per day. Schedule weekly saline infusions for the first month to maintain hydration, serum sodium levels	**Grade 1:** Maintain dose. Rule out other causes, including drug effects. Initiate anti-diarrheal treatment per institutional guidelines **Grade 2:** Rule out other causes including drug effects. Treat per institutional guidelines. Interrupt selinexor until resolved to Grade 1 or baseline For first occurrence, restart selinexor at current dose For ≥ 2nd occurrence, reduce selinexor by 1 dose level **Grade 3:** Delay selinexor until resolved to Grade 1 and the patient is clinically stable, then reduce selinexor dose by 1 dose level

Table 2 Continued

Symptom	Prophylaxis	Treatment
Thrombocytopenia	Weekly office visits with CBC during cycle 1	**Grade 1 or 2 (≥ 50,000/mm^3):** Maintain dose. Rule out other causes including drug effects **Grade 3** without bleeding: Consider platelet growth factors per institutional guidelines and to continue with dose reduction as below: For patients on 80 mg twice weekly: Dose reduce to 100 mg total dose per week For patients on weekly selinexor: Dose reduce by 20 mg **Grade 4** without bleeding: Strongly consider platelet growth factors and transfuse per clinical practice/institutional guidelines. Delay or hold selinexor dosing until platelets recover to Grade 2
Neutropenia	Assessed during weekly office visits with CBC during cycle 1	**Grade 1 or 2:** If absolute neutrophil count of 0.5 to 1.0 × 10^9/L or higher, no intervention is needed. **Grade 3:** If absolute neutrophil count of 0.5 to 1.0 × 10^9/L without fever, consider reducing selinexor by 1 dose level. **Grade 4** If absolute neutrophil count less than 0.5 × 10^9/L OR febrile neutropenia, interrupt selinexor. Monitor until neutrophil counts return to 1.0 × 10^9/L or higher then restart selinexor at 1 dose level lower.

Abbreviations: AEs = adverse events; CBC = complete blood count; NCCN CPGO = National Comprehensive Cancer Network' Clinical Practice Guidelines in Oncology; NK_1 = neurokinin 1

2. Platelets below 25,000/μL, hold treatment or give platelet transfusion support to allow for potential continuance of selinexor.
3. Although not formally indicated in the prescribing information, platelet stimulation growth factors such as romiplostim 10 mcg/kg weekly have been used successfully to reduce the need of transfusions.[14] We considered romiplostim 10 mcg/kg weekly once platelet count was below 50,000/μL.

Fatigue

Fatigue is a common side effect of selinexor in a heavily pretreated population of patients with MM. Addressing the gastrointestinal toxicities referenced above may reduce fatigue from dehydration and nutritional intake. However, if it remains severe and persistent, dose reductions should be considered. Methylphenidate has been studied in cancer-related fatigue, is useful in a subset of patients, and should be considered.[15] Methylphenidate is typically initiated at a starting dose of 5 mg in the morning and at noon, or a comparable dose of one of the long-acting modified-release formulations. The dose usually requires titration until benefits occur or side effects supervene.[16] Most patients experience less fatigue with selinexor at doses well below 60 mg/day, but some require higher doses for improved disease control. Reasonable nonpharmacologic strategies to address fatigue include mild exercise and cognitive behavioral and sleep interventions before dose reductions of selinexor should occur.[17]

Hyponatremia

In the STORM trial, 39% of patients experienced grade 1 hyponatremia with selinexor, and 22% of patients experienced a more severe grade 3 to 4 hyponatremia. The mechanism is not well understood, but it tends to be transient and reversible. Salt tablets or salty snacks (such as salted pretzels) and monitoring the sodium level are both important in managing hyponatremia. Selinexor should be held when the sodium falls below 130 mmol/L and resumed 1 dose level lower when hyponatremia is corrected to above 130 mmol/L (See selinexor prescribing information).

Additional Key Points for Patient Education

1. Instruct patients to take selinexor and other medications (such as dexamethasone and antiemetics) exactly as prescribed. Selinexor is a tablet that should not be broken, chewed, or crushed.
2. If a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If vomiting occurs, advise the patient to take the next dose on the next regularly scheduled day.
3. Serum chemistry labs, as well as a complete blood count, will be regularly monitored on a weekly basis during the first month. Labs such as blood sodium and magnesium should be reviewed before each dose. Body weight will also be monitored at baseline and during treatment, with more frequent monitoring during the first 2 months of treatment.

Table 3 Patient Handout: Suggestions for Nutritional Support While Taking Selinexor

Good nutrition is an important part of your cancer care. While taking selinexor, your appetite may be lower, and you may experience nausea. During the first month or 2 while taking selinexor, try to keep in mind these 3 tips:

1) It is important to focus on eating small, frequent meals or incorporating higher-calorie snacks when able

2) Drink at least 2 liters of fluids per day to lessen nausea, protect your kidney function, and to stimulate your appetite. You should try to drink not only water, but include salt-containing drinks such as sport drinks or Pedialyte.

3) Check your weight daily and focus on more high-calorie snacks if your weight is dropping. Tell your healthcare provider if you are losing more than 5 lbs in a week.

Snacks and Supplements	Calories
McDonald's 4-piece chicken nuggets	150
1 frozen waffle with 1 tbsp. butter and 1 tbsp. syrup	250
English muffin and 1 tbsp. nut butter	250
6 oz. container sweetened yogurt and 1/2 cup granola	300
Plain bagel and 2 tbsp. cream cheese	300
1 chicken drumstick and 1/2 cup mashed potato	400
1 envelope instant oatmeal cooked with 1/2 cup 2% milk, 1 tbsp. brown sugar, 1 tbsp. butter, 1 tbsp. raisins	400
1 one-half ounce chocolate bar (milk or dark) and 1/4 cup of almonds	400
1/2 cup tuna or egg salad sandwich and 1 cup 2% milk	600-700
1/2 cup trail mix and 8 oz. juice	500
Blended shake: 2 tbsp. peanut or almond butter, 1 banana, 1 cup chocolate milk, and 1 scoop protein powder	550-650
Grilled cheese sandwich or quesadilla: 2 slices bread or tortilla, 2 slices cheese, and 2 tbsp. butter	500-700
Add condiments to increase calories 1 tbsp. butter, margarine, vegetable oils (canola, olive, etc.) peanut or almond butter, tahini, mayonnaise, sour cream; 1/4 cup shredded cheese, raisins or other dried fruit, croutons, nuts	100-200 calories

Note: This list was compiled based on information from Cleveland Clinic patient education materials.

4. Advise patients to maintain appropriate fluid and caloric intake throughout, and report a decrease in oral intake immediately.

Conclusion

Although MM remains an incurable disease, there continue to be more options available for patients with relapsed and refractory disease. Selinexor has now been approved in advanced myeloma for patients that have progressed on the currently available immunomodulatory agents, proteasome inhibitors, and CD-38 monoclonal antibodies. Having a new drug is always encouraging both for patients and providers, but poses a unique challenge with an unfamiliar toxicity profile (especially a first-in-class drug), which can only be overcome by gaining familiarity with the drug by repeated usage of the agent. It is not the first time that we have faced similar situations in myeloma treatment as we quickly understood the adverse event management for bortezomib-induced neuropathy, or carfilzomib-related cardiac toxicity, based on our experience in clinical trials. It is time again to embrace a new anti-myeloma drug where our patients could benefit. We urge that patients taking the drug should be monitored carefully to help overcome its unique toxicity profile, which will allow the patients the opportunity to experience the benefit of selenexor-induced prolonged remissions.

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