Title: Selinexor (Xpovio) Dose Optimization: A Retrospective Analysis

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ABSTRACT

Background: Several oral oncolytics are approved at doses that require early and frequent intervention to manage associated toxicities. This retrospective analysis investigated efficacy and safety outcomes of patients initiated on lower doses (≤ 80 mg) of selinexor (Xpovio) compared to those who started at higher doses (> 80 mg). **Material and Method:** All patients who were prescribed selinexor between December 18, 2020 and August 1, 2023 were included. Patients were categorized as less than 80 mg and more than 80mg. The primary endpoint was progression-free survival (PFS). Secondary endpoints included rates of dose interruption, reduction, and discontinuation. The investigators also assessed the total cost of care and waste related to therapy. PFS data was analyzed using a log-rank test. A total of 24 patients were reviewed, 7 in the > 80 mg group and 17 in the ≤ 80 mg arm. **Results:** Patients starting on lower doses of selinexor required fewer dose interruptions, reductions, had lower rates of discontinuation due to adverse events (AEs), and less waste compared to those who were initiated on doses that exceeded 80 mg. The lower dosing did not result in a statistically significant difference in PFS. **Conclusion:** This data suggests that lower initial dosing may improve selinexor's safety profile without compromising efficacy.

INTRODUCTION

Multiple myeloma makes up 1.8% of all new cancer diagnoses with nearly 36,000 new cases per year.[1] The annual incidence of diffuse large B-cell lymphoma (DLBCL) is 5.5 per 100,000 individuals.[2] Both disease states are more prevalent in males, with African Americans at the highest risk for multiple myeloma and Hispanics for diffuse large B-cell lymphoma.

Selinexor is an inhibitor of exportin 1, a nuclear export protein that transports polypeptides that regulate cell growth and apoptosis from the nucleus to the cytoplasm.[3] Exportin 1 is overexpressed in multiple myeloma and DLBCL, leading to increased export of these proteins and resultant abnormal cell growth. Therefore, inhibition of this exporter causes accumulation of tumor suppressor proteins in the nucleus, oncoprotein reduction, cell cycle arrest, and cancer cell apoptosis.

In September 2022, Texas Oncology's pharmacy and therapeutics (P&T) committee issued a recommendation to start at doses no greater than 80 mg and permitted ramp up dosing based on patient tolerability. For the treatment of multiple myeloma, selinexor is dosed at 100 mg once weekly in combination with bortezomib and dexamethasone and at 80 mg on days 1 and 3 of each week in combination with dexamethasone per the package insert.[4] For diffuse large B-cell lymphoma, the recommended dose is 60 mg on days 1 and 3 of each week. At these FDA-approved doses, patients frequently require dose interruptions, reductions, and discontinuation of therapy due to adverse effects, namely thrombocytopenia, fatigue, appetite loss, nausea, and neutropenia.[5-7]

The BOSTON and STORM trials evaluated the use of selinexor in previously treated multiple myeloma. STORM was a phase 2b study that evaluated selinexor 80 mg twice weekly (160 mg total weekly dose) in combination with 20 mg of dexamethasone. The rate of dose interruption was 65%, the rate of dose reduction was 53%, and the rate of discontinuation secondary to AEs was 27%. BOSTON was a randomized, open-label, phase 3 trial that evaluated selinexor 100 mg once weekly in combination with bortezomib once per week, and dexamethasone 20 mg twice weekly. The rates of dose interruption, dose reduction, and discontinuation due to adverse effects were 83%, 64%, and 19%, respectively. The SADAL trial was a phase 2b study that evaluated selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma. The rates of dose interruption, dose reduction, and discontinuation due to AEs were 61%, 49%, and 17%, respectively.

The objective of this study was to determine if starting at a reduced dose of selinexor increased the patient's length of therapy, reduced waste, and reduced incidence of dose interruption, reduction, and discontinuation without compromising progression-free survival (PFS).

METHODOLOGY

Texas Oncology is responsible for the cancer care of approximately 70,000 new patients annually across the state, which occurs at over 280 centers with 45 sites offering pharmacy services. It is the largest private community oncology group in the country. This retrospective chart review included all patients who had been prescribed selinexor at Texas Oncology and had it dispensed at a Texas Oncology pharmacy from January 2020 until August 2023. Patients were included if they had been prescribed selinexor on or before August 1, 2023. Patients were excluded if they did not fill selinexor at a Texas Oncology pharmacy or the drug was never initiated. Before the research study was conducted, the Texas Oncology Privacy Board approved it on November 30, 2023.

The investigators generated a list of all patients who were prescribed selinexor at all Texas Oncology pharmacy sites utilizing the EMR. Chart reviews were performed identifying the following items: age, sex, race, performance status, practice location, ICD-10 diagnosis, selinexor strength prescribed, quantity prescribed, number of refills prescribed, other drugs prescribed in the same regimen, date prescribed, date started, date(s) held and reasoning, date(s) dose was adjusted and reasoning, date of discontinuation and reasoning, if applicable, adverse events reported, and line of therapy. Patients were stratified into one of two groups based on whether they were initiated at a dose less than or equal to 80 mg or greater than 80 mg.

The primary endpoint was PFS, defined as time from initiation of selinexor to disease progression per physician assessment or death. Secondary endpoints included rate of dose interruptions, reductions, and discontinuation as well as incidence of adverse effects and duration of therapy. The investigators also calculated the total cost of treatment, defined as the wholesale acquisition cost (WAC) for selinexor throughout the duration of therapy, in addition to waste associated with dose reductions.

Kaplan-Meier survival analysis of PFS was undertaken, using log-rank tests; pairwise evaluations were made between the two groups: patients who started at an initial dose of more than 80 mg and patients started at an initial dose lower than 80 mg. This was followed up by a

descriptive correlational analysis of dose reductions, interruptions, and discontinuations. The average cost of treatment was analyzed using a WAC of $30,670 for a 28-day supply. Waste was calculated for the nine patients that required dose reduction, which was determined by quantifying the remaining tablets when a patient dose was reduced. One patient in the ≤ 80 mg group was excluded from the cost analysis as their prescription was transferred to an outside pharmacy. The data cutoff utilized for statistical analysis was January 20, 2024. Statistical analysis was carried out using DATAtab: Online Statistics Calculator on February 1, 2024.[8]

RESULTS

The researchers identified thirty patients across Texas Oncology who had been prescribed selinexor. Six of these patients never started therapy for various reasons such as insurance denial or a decision to pursue alternative therapies. Twenty-four patients met the eligibility criteria and were included in the analysis. Most patients were white, with an average age of 71 years, and most patients were on their fifth line of therapy or greater (Table 1). Baseline characteristics differed between the two groups. The group with initial doses greater than 80 mg had a higher percentage of female patients and were more heavily pretreated. The median initial dose prescribed for the higher dosed group was 100 mg and for the lower dosed group was 60 mg.

At the data cutoff (January 20, 2024), five patients were still on therapy with selinexor, one (14%) in the > 80 mg group and four (24%) in the ≤ 80 mg arm. The median PFS was 80 days (95% CI 47-93) for patients who started on higher doses compared to 120 days (95% CI 61-165) for those who started at lower doses (Figure 1). In the group with high initial doses, the primary reason for discontinuation was adverse effects, and in the arm with lower doses, discontinuation was most frequently secondary to progression or death (Table 2). Four (57%) patients in the > 80 mg group required dose reductions, with an incidence of seven dose decreases in the group. Four (24%) patients in the ≤ 80 mg group required dose reduction with a total of six dose decreases across the group. In the group with higher initial doses, the median number of days that doses were held was 15.2 and 9.4 for the lower dose group.

Ten (59%) patients in the ≤ 80 mg group and six (86%) patients in the > 80 mg group reported an adverse event related to therapy. The most common AEs were nausea, fatigue, and thrombocytopenia. The most common causes for held doses were thrombocytopenia, neutropenia, and vision changes/cataracts. The most frequent reasons for dose reduction were nausea, thrombocytopenia, and neutropenia. Thrombocytopenia was the most common cause of discontinuation among all AEs.

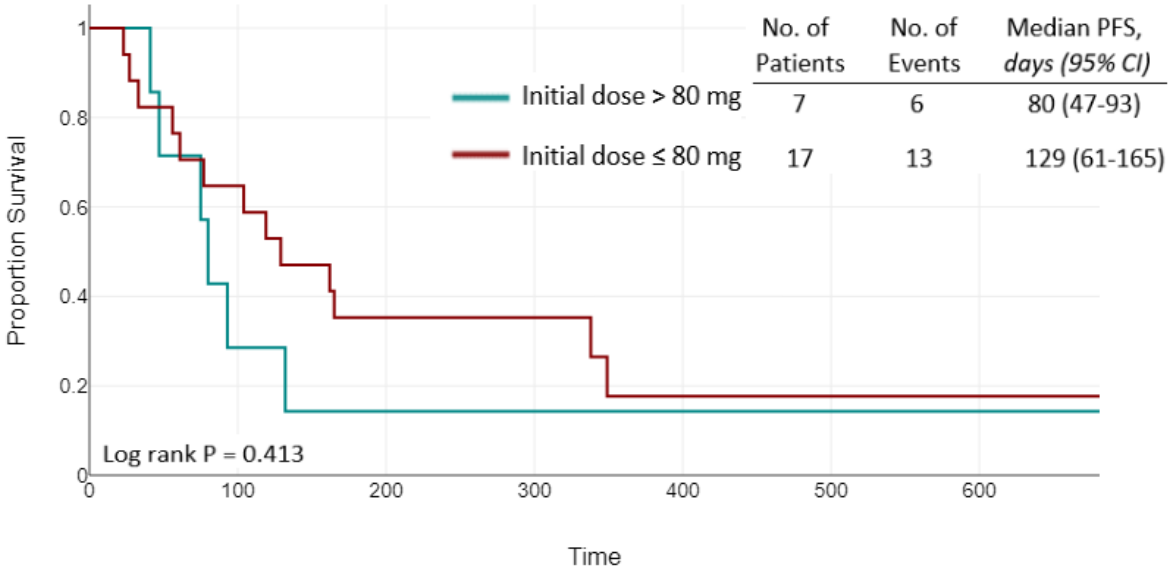
For the > 80 mg group, the average total cost of treatment per patient was $122,680 with an average of $13,417.88 in waste per individual (Table 3). In the group that started at ≤ 80 mg, the total cost of treatment was $134,181.25 per patient with a mean of $1,533.50 in waste per patient. In the higher-dosed group, 7.6% of the total cost of treatment was wasted compared to 0.8% wasted in the lower-dosed group.

Table 1: Baseline Patient Characteristics

Characteristic	Initial Dose ≤ 80 mg *n = 17* *no. (%)*	Initial Dose > 80 mg *n = 7* *no. (%)*
Age, years		
Median (range)	67 (48-90)	73 (67-82)
Age ≥ 65	13 (77%)	7 (100%)
Sex		
Male	10 (59%)	2 (29%)
Female	7 (41%)	7 (71%)
Race		
White	14 (82%)	6 (86%)
Black or African American	2 (12%)	1 (14%)
Asian	1 (6%)	0
Ethnicity		
Hispanic or Latino	4 (24%)	1 (14%)
Not Hispanic or Latino	13 (76%)	6 (86%)
Diagnosis		
Multiple Myeloma	16 (94%)	7 (100%)
Diffuse Large B-cell Lymphoma	1 (6%)	0
ECOG Performance Status Score		
0	6 (35%)	2 (29%)
1	9 (53%)	5 (71%)
Not Reported	2 (12%)	0
No. of previous lines of systemic therapy		
2	1 (6%)	0

3	4 (23.5%)	0
4	2 (12%)	0
5	4 (23.5%)	2 (29%)
6+	6 (35%)	5 (71%)
Initial Dose, mg		
40	3 (18%)	0
50	1 (6%)	0
60	8 (47%)	0
80	5 (29%)	0
100	0	5 (71%)
160	0	2 (29%)

Figure 1: Kaplan-Meier estimates of progression-free survival



	Total N	N of Event	N of Censored	% of Censored
A	7	6	1	14.29%
B	17	13	4	23.53%

Table 2: Secondary Endpoints

Endpoint	Initial Dose ≤ 80 mg *n = 17* *no. (%)*	Initial Dose > 80 mg *n = 7* *no. (%)*
Dose Interruptions (total)	13	11
Patients with interruption	5 (29)	5 (71)
Total days held	151	91
Average days held	9.4	15.2
Median days held	0	10.5
Reason for Holding:		
Thrombocytopenia	3	7
Vision change/cataract	3	1
Neutropenia	2	2
Infection	1	1
LFT elevation	1	0
Diarrhea	1	0
Hospitalization	1	0
Dose Reductions (total)	4	7
Patients requiring reduction	4 (24)	4 (57)
Reason for Reducing:		
Nausea/Vomiting	2	2
Thrombocytopenia	1	2
Neutropenia	0	2
Fatigue	0	1
Unknown	1	0
Discontinuation (total)	13 (76)	6 (86)
Secondary to ADEs	0	3 (50)

Table 3: Financial Analysis

Endpoint	Initial Dose ≤ 80 mg *n = 17* *no. (%)*	Initial Dose > 80 mg *n = 7* *no. (%)*
Total Cost of Treatment, $ *All patients*	2,146,900	858,760
Average per patient	134,181.25	122,680
Total Cost of Treatment, $ *Dose reduced patients*	950,770	705,410
Average per patient	190,154	176,352.50
Total Waste, $*	7,667.50	53,672.50
Average per patient	1,533.50	13,417.88

*Waste calculated for the 9 patients that required dose reduction. One patient in the ≤ 80 mg group was excluded from the cost analysis as they were transferred to an outside pharmacy.

Table 3: Safety

Adverse Drug Event	**≤ 80 mg** *n = 17* *n (%)*	**> 80 mg** *n = 7* *n (%)*
Nausea	5 (29.4)	5 (71.4)
Fatigue	6 (35.3)	3 (42.9)
Thrombocytopenia	2 (11.8)	4 (57.1)
Neutropenia	1 (5.9)	4 (57.1)
Anemia	3 (17.6)	1 (14.3)
Appetite loss	3 (17.6)	1 (14.3)
Weakness	3 (17.6)	1 (14.3)
Diarrhea	3 (17.6)	1 (14.3)
Vision change/cataract	3 (17.6)	1 (14.3)
Constipation	2 (11.8)	0
Vomiting	1 (5.9)	1 (14.3)
Pneumonia	1 (5.9)	1 (14.3)

DISCUSSION

In this retrospective chart review comparing outcomes of patients who started on doses exceeding 80 mg with those starting on doses of 80 mg or less, there was not a statistically significant difference in PFS. Patients who started on lower doses had fewer dose interruptions, dose reductions, discontinuations, AEs, and less waste. This data suggests that reduced dose intensities may result in a better quality of life without sacrificing longevity. The p-value of > 0.05 confirmed that dose reduction does not have a statistically significant impact on PFS.

Texas Oncology patients who started at the higher labeled dosing had similar rates of dose interruption and reduction compared to patients in the BOSTON, STORM, and SADAL trials.[5-7] Discontinuation rates due to AEs were much higher in Texas Oncology patients compared to the aforementioned trials, likely due to the small sample size. Additionally, the clinical trial criteria for discontinuation were standardized and more stringent than what is observed in practice.

Recent studies are already utilizing lower doses of selinexor.[9-11] The SIENDO trial utilized a dose of 80 mg weekly in patients with endometrial cancer.[9] An ongoing phase 2b trial studying selinexor in combination with carfilzomib, daratumumab, or pomalidomide is utilizing selinexor 60 mg, 80 mg, or 100 mg weekly for multiple myeloma.[10] Another ongoing phase 1b/2 study for multiple myeloma involves selinexor at 40 mg or 60 mg in combination with the novel agent mezigdomide.[11] Florida Cancer Specialists and Research Institute performed a retrospective analysis and found that initiating selinexor at doses ≤ 80 mg in addition to

providing upfront antiemetics resulted in a significant increase in time to treatment failure, a lower incidence of dose-limiting toxicities, and less discontinuations secondary to adverse effects or progression.[12]

Multiple myeloma patients are at a particularly high risk for financial toxicity secondary to the lifelong need for treatment and the frequent use of novel therapies. Based on the findings of this study, there is the potential for a cost savings of nearly $12,000 per patient by initiating selinexor at a lower dose. This dosing strategy can result in significant cost savings while maintaining efficacy and minimizing negative outcomes.

A strength of this study is the inclusion of not only safety and tolerability outcomes but the consideration of the impact on efficacy as well. The inclusion of financial analyses of waste and total costs were another benefit of this study and especially relevant for privately owned practices such as Texas Oncology.

There are limitations to this analysis that must be considered, including the retrospective nature of the study, unknown patient compliance, and several unbalanced baseline characteristics between groups. This study is also limited by the possibility of individual treatment breaks that were not documented and therefore not accounted for. In addition, the small sample size may have been a contributor to the lack of significance. Finally, some Texas Oncology physicians have been utilizing selinexor as bridging therapy, which may have altered the PFS somewhat for patients who started therapy more recently.

CONCLUSION

The authors conclude that initiating selinexor at doses that do not exceed 80 mg reduces the incidence of dose interruption, reduction, and discontinuation while maintaining efficacy of therapy in terms of PFS and translating to significant cost savings. Thus, we can improve tolerance to selinexor without compromising efficacy. This analysis and data from recent studies reaffirm the P&T committee's decision to recommend that selinexor be initiated at doses no more than 80 mg.

- Patients initiated on lower doses experienced fewer adverse events than those started at higher doses (59% vs 86%)
- 24% of patients in the ≤ 80 mg group required dose reduction compared to 57% in the > 80 mg arm
- Selinexor was held for lower median duration when started at lower doses compared to higher doses (9.4 vs 15.2 days)
- In the group with high initial doses, the primary reason for discontinuation was due to adverse effects, and in the arm with lower doses, discontinuation was most frequently secondary to progression or death
- There was not a statistically significant difference in PFS between patients who started selinexor at doses ≤ 80 mg compared to those who were initiated at doses > 80 mg
- Initiating selinexor at lower doses results in a potential cost savings of nearly $12,000 per patient

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