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Original article

Prolonged Lenalidomide Induction Does Not Significantly Impair Stem Cell Collection in Multiple Myeloma Patients Mobilized With Cyclophosphamide or Plerixafor: A Report From The Covid Era

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Abstract

We investigated whether prolonged lenalidomide treatment impairs stem cell collection among patients with multiple myeloma mobilized with plerixafor or cyclophosphamide. There was no correlation between the duration of lenalidomide therapy and the number of stem cells collected, suggesting that prolonged treatment with lenalidomide is not a significant barrier to stem cell collection in the context of modern mobilization regimens.

Introduction: Induction therapy for multiple myeloma is traditionally capped at 6 cycles of lenalidomide due to concerns that longer treatment compromises the ability to collect sufficient stem cells for autologous stem cell transplantation (ASCT). However, during the COVID-19 pandemic, many of our patients received prolonged lenalidomide induction due to concerns about proceeding to ASCT. We investigated whether prolonged induction with lenalidomide affects the efficacy of stem cell collection among patients mobilized with cyclophosphamide and/or plerixafor. **Patients and methods:** This single center, retrospective study included patients who were treated with lenalidomide induction regimens, received mobilization with cyclophosphamide or plerixafor, and underwent apheresis in preparation for ASCT. 94 patients were included, 40 of whom received prolonged induction with >6 cycles of lenalidomide containing regimen. **Results:** Patients who received prolonged induction were more likely to require >1 day of apheresis (38% vs. 15%; OR 3.45; $P = .0154$), and there was a significant correlation between the duration of lenalidomide treatment and the apheresis time required to collect sufficient cells for transplant ($R^2 = 0.06423$, $P = .0148$). However, there was no significant difference between patients who received prolonged induction and those who did not with respect to $CD34^+$ stem cell yields at completion of apheresis (9.99 vs. 10.46 cells/Kg, $P = .5513$) or on the first day of collection (8.29 vs. 9.59 cells/Kg, $P = .1788$). **Conclusion:** Among patients treated with >6 cycles of lenalidomide, mobilization augmented with cyclophosphamide and/or plerixafor will likely facilitate sufficient stem cell harvest to permit ASCT.

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Introduction

Multiple myeloma (MM) is a neoplastic proliferation of plasma cells in the bone marrow that accounts for 1%-2% of malignancies in the United States.[1] The most commonly used induction regimen for MM consists of bortezomib, lenalidomide, and dexamethasone (VRd), which is often followed by high dose melphalan and stem cell rescue with autologous stem cell transplantation (ASCT).[2] More recently, carfilzomib, lenalidomide, and dexamethasone (KRd) has emerged as an effective alternative induction regimen,[3] and the anti-CD38 monoclonal antibody daratumumab has further improved

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induction responses.[4] Regardless of the initial therapy, induction is typically limited to 3-6 cycles of a lenalidomide containing regimen for transplant eligible patients in order to permit successful $CD34^+$ stem cell harvest and ASCT.[2] High dose melphalan with ASCT significantly prolongs progression free survival (PFS) and overall survival (OS) compared to maintenance therapy alone,[5,6] but ASCT requires peripheral-blood mobilization and collection of a sufficient number of $CD34^+$ stem cells to facilitate recovery from high-dose chemotherapy. Early studies suggested that lenalidomide therapy impaired stem-cell collection,[7-13] and therefore, induction is usually capped at 6 cycles to prevent prolonged lenalidomide exposure.

Marrow-resident $CD34^+$ stem cells can be mobilized into the peripheral blood with exogenous administration of Granulocyte-Colony Stimulating Factor (G-CSF) and are thus able to be harvested with apheresis.[14] G-CSF mobilization alone often yields an adequate peripheral blood $CD34^+$ cell harvest, but early studies among patients mobilized with G-CSF identified an inhibitory effect of lenalidomide on stem cell collection.[7-13] However, in those who fail to mobilize sufficient cells, or those who are predicted to mobilize poorly, the addition of cyclophosphamide prior to G-CSF mobilization or the addition of plerixafor, a CXCR4 antagonist, improves the chances of successful progenitor cell harvest.[14] Mobilization with cyclophosphamide and/or plerixafor is routinely employed at our center, and we have had very few patients in whom collection of sufficient cells for transplant has failed. This is consistent with studies suggesting that use of cyclophosphamide[15-19] and/or plerixafor[20-23] enables the majority of lenalidomide treated patients to collect adequate cells for transplant, even among those treated with more than 6 cycles of lenalidomide.[24] However, few studies have explored the impact of prolonged induction in substantial number of patients, and no studies have described the impact of prolonged induction in patients mobilized exclusively with the assistance of cyclophosphamide or plerixafor. Therefore, whether prolonged induction with more than 6 cycles of lenalidomide significantly impairs stem cell collection when rationale use of cyclophosphamide and/or plerixafor is employed remains unclear. As response to induction deepens with increasing cycles,[25] whether there is a need to restrict the number of cycles of lenalidomide in order to permit ASCT is of significant clinical interest.

During the COVID-19 pandemic, the myeloma community has recommended delaying ASCT,[26-29] which can extend induction therapy beyond the typical 3 to 6 months. In accordance with these recommendations, our institution performed no ASCTs for multiple myeloma patients in April or May of 2020, and the number of ASCTs performed in the following months was historically low as well. This created an unprecedented natural experiment in which a greater than expected number of patients received prolonged inductions with more than 6 cycles of lenalidomide containing regimen. In an effort to shorten hospital stays during the pandemic and shorten time spent in our infusion center, we also utilized plerixafor for stem cell mobilization more often. We therefore investigated, in a population of patients mobilized exclusively with the assistance of cyclophosphamide or plerixafor, whether prolonged induction with lenalidomide, defined as receiving more than 6 cycles of lenalidomide containing regimen, affected the efficacy of $CD34^+$ stem cell collection. We hypothesized that prolonged induction would have minimal effect on $CD34^+$ stem cell yields among cyclophosphamide or plerixafor treated patients, but that prolonged induction would likely suppress pre-apheresis cell counts and extend the apheresis time required to collect sufficient cells for transplant.

Patients and Methods

Study Design and Conduct

We conducted a retrospective, single center study to assess the impact of prolonged induction with lenalidomide, defined as treatment with >6 cycles of lenalidomide containing regimen, on $CD34^+$ stem cell harvest in patients with multiple myeloma undergoing progenitor-cell apheresis for up-front consolidation with high dose melphalan and ASCT. One cycle of lenalidomide was defined as a 28-day period (with lenalidomide received for 21 out of 28 days) in which a patient received any treatment containing lenalidomide, such as VRd or KRd. Dose reductions of chemotherapy were permitted at the discretion of the prescribing physician. We collected data on the number of cycles of lenalidomide patients received prior to mobilized collection by apheresis, as well as data on patient characteristics which are known to or may plausibly affect stem cell collection. For outcome variables, we collected data on the total number of $CD34^+$ cells collected at the completion of apheresis, the number of $CD34^+$ cells collected on the first day of apheresis, and the length of time patients underwent apheresis. Data was collected by chart review of electronic medical records after approval from our Institutional Review Board (IRB) via IRB-exempt status.

Patients and Eligibility Criteria

Eligible patients were $\geq$ 18 years of age at the time of multiple myeloma diagnosis and underwent mobilization and apheresis to collect $CD34^+$ cells for ASCT at the University of Maryland Marlene & Stewart Greenebaum Comprehensive Cancer Center between October 1, 2019 and July 1, 2021. Eligible patients were mobilized with G-CSF in combination with cyclophosphamide, plerixafor, or both, per physician preference, following institutional protocols, with the goal of collecting sufficient cells for transplantation (target: 6×10^6 $CD34^+$ cells/Kg; minimum 4×10^6 $CD34^+$ cells/Kg). In patients who received cyclophosphamide mobilization, there was no limit on the number of apheresis sessions permitted to collect the target cell harvest; for patients who did not receive cyclophosphamide, a maximum of 2 apheresis sessions were employed. Patients were included in the analysis regardless of whether subsequent transplantation took place. Patients treated with 2 or more cycles of any regimen that did not include lenalidomide were excluded. This excluded several patients who had received more than 1 cycle of cyclophosphamide/bortezomib/dexamethasone (CyBorD) or more than 1 cycle of daratumumab/pomalidomide/dexamethasone (DPd).

Stem Cell Mobilization and Collection

As per our institutional standard, the choice of mobilization was made at the physician's discretion, with an increased utilization of chemotherapy-free mobilization (using plerixafor only) employed early in the COVID-19 pandemic to minimize patient risk and optimize apheresis scheduling. Our standard regimens include G-CSF with plerixafor (G-P), dosed according to the Mozobil®

Package Insert, and low-dose cyclophosphamide (1.5 grams/m^2) followed by G-CSF 10 mcg/Kg/day through harvest by apheresis (Cy-G). Stem cell collection by apheresis with G-P began on Day 5 and continued through Day 6, if required. Collection after Cy-G began on or after Day 9, depending on peripheral blood CD34 cell ($_{PB}$CD34)-based predicted yield, and continued until the target was reached or diminishing daily yield predicted futility of further collections. The stem-cell target was predetermined by the prescribing physician based on institutional norms; our standard target for patients with multiple myeloma is 6×10^6 CD34 cells/Kg for patients older than 60 years, and 10×10^6/Kg for those 60 years and younger. A CBC was obtained for patients on the day prior to anticipated apheresis, ie, Day 4 with G-P mobilization and Day 8 with Cy-G; the $_{PB}$CD34 was also obtained when feasible (WBC of at least 2000/mm^3) immediately prior to apheresis. The pre-apheresis WBC, pre-apheresis platelet count, and $_{PB}$CD34 were from these tests. In patients mobilized with Cy-G, plerixafor rescue was employed at the discretion of the collecting physician, generally if mobilization kinetics were sluggish or if the first day collection predicted a suboptimal total stem cell harvest.

Statistical Analysis

We used descriptive statistics to summarize continuous variables and we used counts and percentages to express categorical variables. Normality of continuous variables was assessed by the D'Agostino and Pearson test. Continuous variables which were normally distributed were compared using student's t test (two tailed) or ANOVA, as appropriate, and variability was summarized using standard error of the mean. Continuous variables which were not normally distributed were compared using Mann-Whitney test and data was described as median (range) or 95% confidence intervals. We used Chi-square test or Fisher's exact test, as appropriate, to compare counts of categorical variables. Correlation was assessed by univariate analysis in which we calculated the coefficient of determination (R^2) and the *P* value of the slope. Outliers were identified by visual inspection of scatter plots. For multivariate analysis, whether a patient received multiple days of apheresis was considered a dichotomous variable, thus we ultilized multivariate logistic regression to examine factors associated with multiple apheresis sessions. We utilized multivariate linear regression for the number of $CD34^+$ cells collected, which was considered a continuous dependent variable. No co-variates included in the same model demonstrated significant collinearity, defined as $R > 0.5$ assessed by scatter plots prior to including them in the model. The variance inflation factors (VIFs) of all co-variates, included in all models, were less than 1.20. For all tests, a *P* value of $< .05$ was considered significant. Statistical analysis was performed using GraphPad Prism version 9.2.0.

Results

Patients and Collection

We identified 94 patients with multiple myeloma who were treated with a lenalidomide-containing induction regimen prior to G-CSF-mobilized $CD34^+$ cell harvest by apheresis. All patients received cyclophosphamide, plerixafor, or both to augment mobilization. In our cohort, 54 patients (57%) received 4-6 cycles of lenalidomide, 30 patients (32%) received 7-8 cycles, and 10 patients (11%) received 9 or more cycles. The highest number of induction cycles received was 13. We separated patients into those who had received "Standard induction" (SI) with 4-6 cycles of lenalidomide (n = 54, 57%) and those who had received "Prolonged Induction" (PInd) with >6 cycles (n = 40, 43%). We compared clinical characteristics across cohorts (Table 1). Overall, cohorts were highly similar and were well balanced based on characteristics at diagnosis, including demographics (age, sex, race), markers of bone marrow function (marrow cellularity and plasma-cell replacement, and peripheral blood hemoglobin and platelet counts), and chemical markers of disease (eGFR, calcium, and LDH) (Table 1). Five patients in our study were older than 70 (1 aged 71 and 4 aged 72). ISS stage did not significantly differ between SI and PInd groups (Table 1). Fewer patients with high-risk disease received PInd, which neared statistical significance (43% vs. 25%, $P = .0742$); suggesting a hesitancy to extend induction in patients with high-risk disease.

Coincident diabetes,[30] prior radiation therapy,[31] and the presence of osteolytic lesions[32] have been previously shown to negatively impact stem cell mobilization and collection. There were no significant differences in frequency of these characteristics between the SI or PInd cohorts (Table 1). The distribution of patients who received VRd, KRd, or both was similar between cohorts, and there was no significant difference in the frequency of patients who received daratumumab (Table 1). Cohorts were well balanced with respect to whether patients received cyclophosphamide, plerixafor, or both for mobilization (Table 1). Only 1 of 94 patient collections (1.1%) failed to provide the minimum number of $CD34^+$ cells required for transplant (4×10^6 $CD34^+$ cells/Kg, our institutional standard). 67/94 (71%) of patients collected enough cells to safely undergo 2 transplants (8×10^6 $CD34^+$ cells/Kg). 23/94 patients (24%) of patients completed multiple days of apheresis. The majority of these patients (21/23) received 2 days of apheresis, though 1 patient received 3 days of apheresis and 1 patient received 4 days.

Clinical Characteristics and Pre-Apheresis Counts Correlate With Apheresis Time and $CD34^+$ Cell Yield

We explored whether the duration of lenalidomide exposure affected stem cell collection outcomes by examining 3 parameters: the total number of $CD34^+$ stem cells collected at the completion of apheresis (C_T), the number of $CD34^+$ cells collected on the first day of apheresis (C_{D1}), and the total minutes of apheresis that a patient completed across all apheresis sessions (A_{Min}). C_T provides a measure of whether apheresis collects sufficient cells to be successful but is highly influenced by the use of subsequent-day plerixafor when the first day-yield predicts an otherwise inadequate total harvest. Examining C_{D1} resolves this issue. C_T and C_{D1} were measured in $CD34^+$ cells x 10^6 /Kg body weight. A_{Min}, by measuring the total time patients undergo collection by apheresis, provides a measure of apheresis efficiency and cost, though ultimately its clinical significance is less than that of the stem-cell yield.

We first examined whether factors which have been previously established to affect collection outcomes correlated with C_T, C_{D1}, or A_{Min} in our data set. Factors which have been previously established to affect the success of $CD34^+$ cell collection include age[15], bone marrow cellularity[14], pre-mobilization WBC[32], pre-apheresis

Table 1 Patient Characteristics

	Standard Induction (SI) [a]	Prolonged Induction (PInd)[a]	*P* value [b]
Population, n (%)	54 (57)	40 (43)	
Median age (range), years[c]	58 (28-72)	61 (44-72)	.2561
Mean age (SEM, n)	58, (1.3, 54)	60, (1.1, 40)	.1967
Sex, n (%)	Male: 30 (56)	Male: 23 (58)	>.9999
	Female: 24 (44)	Female:17 (42)	
Race, n (%)	White: 26 (48)	White: 18 (45)	.1787
	Black: 22 (41)	Black: 20 (50)	
	Asian: 5 (9)	Asian: 0 (0)	
	Latino: 1 (2)	Latino: 2 (5)	
Bone marrow cellularity % [d], median (range, n)	60 (30-100, 46)	60 (5-100, 37)	.5512
Bone marrow plasma cell % [d], median (range, n)	70 (5-99, 51)	60 (5-100, 40)	.4699
Hemoglobin g/dL [d], mean (SEM, n)	10.77 (0.36, 53)	11.05 (0.32, 39)	.5846
Platelets K/mcL [d], mean (SEM, n)	217 (11.8, 53)	221 (8.5, 39)	.8114
Diabetes [d], n (%)	Present: 9 (17)	Present: 5 (12)	.7708
	Absent: 45 (83)	Absent: 35 (88)	
eGFR [d], n (%), mL/min/1.73 m^2	>60: 36 (67)	>60: 33 (83)	.1025
	30-60: 11 (20)	30-60: 4 (10)	
	<30: 3 (6)	<30: 0 (0)	
	Not evaluable/unknown: 4 (7)	Not evaluable/unknown: 3 (8)	
Calcium [d] mg/dL, median (range, n)	9.3 (7.7-13.7, 43)	9.1 (8.2-12.0, 37)	.4963
LDH [d] units/L, median (range, n)	202 (88-995, 32)	257 (90-1205, 24)	.1997
Cytogenetic risk [d], n (%)	High risk: 23 (43)	High risk: 10 (25)	.0742
	Standard risk: 26 (48)	Standard risk: 28 (70)	
	Not evaluable/unknown: 5 (9)	Not evaluable/unknown: 2 (5)	
ISS Stage [d], n (%)	Stage I: 22 (41)	Stage I: 17 (43)	.7910
	Stage II: 13 (24)	Stage II: 14 (35)	
	Stage III: 5 (9)	Stage III: 5 (13)	
	Not evaluable/unknown: 14 (26)	Not evaluable/unknown: 4 (10)	
Osteolytic lesions [d], n (%)	Present: 30 (56)	Present: 23 (58)	>.9999
	Absent: 24 (44)	Absent: 17 (42)	
Induction chemotherapy, n (%)	VRd: 42 (78)	VRd: 31 (78)	.3605
	KRd: 9 (17)	KRd: 4 (10)	
	VRd and KRd: 3 (6)	VRd and KRd: 5 (12)	
Radiation history, n (%)	Present: 10 (19)	Present: 11 (27)	.3265
	Absent: 44 (81)	Absent: 29 (73)	
Daratumumab exposure, n (%)	Received: 4 (7)	Received: 5 (12)	.4884
	Did not receive: 50 (93)	Did not receive: 35 (88)	
Mobilization regimen [e], n (%)	Cyclophosphamide: 21 (39)	Cyclophosphamide: 17 (43)	.4650
	Plerixafor: 25 (46)	Plerixafor: 14 (35)	
	Cyclophosphamide + Plerixafor: 8 (15)	Cyclophosphamide + Plerixafor: 9 (23)	

[a] Standard induction (SI) was defined as 4-6 cycles of lenalidomide containing regimen, Prolonged induction (PInd) was defined as >6 cycles of lenalidomide containing regimen
[b] Fisher's exact test, chi square test, student's t test, or Mann-Whitney test as appropriate
[c] Although data was normally distributed, comparison of medians is also shown in accordance with convention. Age reflects patient age at first apheresis.
[d] Obtained or present at diagnosis
[e] All mobilization regimens also utilized G-CSF

Table 2 Correlation of Clinical Characteristics With Stem Cell Yield and Apheresis Time

	Total CD34$^+$ Cells Collected (C_T)	CD34$^+$ Cells Collected On The First Day Of Apheresis (C_{D1})	Apheresis Minutes (A_{Min})
Age at apheresis	Y = -0.1402*X + 18.46	Y = -0.1404*X + 17.41	Y = 1.818*X + 272.8
	R^2 = 0.08811	R^2 = 0.05587	R^2 = 0.005834
	P = .0039	*P* = .0233	*P* = .4718
Bone marrow cellularity %, at diagnosis	Y = 0.02556*X + 8.700	Y = 0.02181*X + 7.829	Y = 0.2254*X + 362.5
	R^2 = 0.02340	R^2 = 0.01165	R^2 = 0.0008269
	P = .1674	*P* = .3314	*P* = .7976
WBC immediately prior to first apheresis	Y = -0.01311*X + 10.51	Y = 0.009683*X + 8.824	Y = 0.3704*X + 395.8
	R^2 = 0.003619	R^2 = 0.001355	R^2 = 0.0007537
	P = .5646	*P* = .7247	*P* = .7928
Platelets immediately prior to first apheresis	Y = 0.003474*X + 9.591	Y = 0.01689*X + 6.538	Y = -0.7397*X + 494.3
	R^2 = 0.005394	R^2 = 0.07505	R^2 = 0.08847
	P = .4866	*P* = .0082	*P* = .0042
Peripheral CD34/mcl collected before start of apheresis	Y = 0.03505*X + 8.772	Y = 0.05638*X + 6.731	Y = -2.242*X + 469.5
	R^2 = 0.1073	R^2 = 0.1863	R^2 = 0.1644
	P = .0015	*P* < .0001	*P* < .0001

Significant *P* values (*P* < .05) are shown in bold.

and pre-mobilization platelet count,[15,33,34] and peripheral CD34$^+$ cell count,[33,35,36] collected immediately prior to the first apheresis. Collection of pre-apheresis counts is routine practice at our institution, as peripheral CD34$^+$ cell count can be used to identify patients requiring additional treatment with mobilization therapies.[33,35,36] Results are shown in Table 2. Age at apheresis significantly correlated with reduced C_T and C_{D1} (R^2 = 0.08811, *P* = .0039 and R^2 = 0.05587, *P* = .0233, respectively). Platelet count prior to apheresis was significantly associated with increased C_{D1} and reduced apheresis time (R^2 = 0.07505, *P* = .0082 and R^2 = 0.08847, *P* = .0042, respectively) but there was no significant correlation between platelet count and C_T (R^2 = 0.005394, *P* = .4866) (Table 2). Higher peripheral CD34$^+$ cell counts were significantly associated with increased C_T and C_{D1} (R^2 = 0.1073, *P* = .0015 and R^2 = 0.1863, *P* < .0001, respectively), as well as reduced A_{Min} (R^2 = 0.1644, *P* < .0001). There was no significant correlation between pre-apheresis WBC or bone marrow cellularity and C_T, C_{D1}, or A_{Min} (Table 2). These findings support higher peripheral CD34$^+$ cell and platelet counts, when obtained before apheresis, as predictors of harvest success, and advanced age as a predictor of less successful harvest.

With respect to additional characteristics which have been previously shown to affect apheresis, patients with and without a documented diagnosis of diabetes collected similar numbers of CD34+ stem cells in total and on the first day of apheresis, and they underwent apheresis for a similar number of minutes (10.16 vs. 10.81 cells x 10^6 /Kg, *P* = .5526, 9.07 vs. 8.69 cells x 10^6 /Kg, *P* = 0.7734, and 325 vs. 351 minutes, *P* = .9518, respectively). C_T, C_{D1}, and A_{Min} were also similar between patients who had prior radiation therapy and those who did not (10.28 vs. 10.18 cells x 10^6 /Kg, *P* = .9178, 8.87 vs. 9.50 × 10^6 cells/Kg, *P* = .5734, and 329 vs. 324 minutes, *P* = .4391, respectively). There was also no significant difference in C_T, C_{D1}, or A_{Min} between patients who did or did not have lytic lesions (9.65 vs. 10.72 × 10^6 cells/Kg, *P* = .1693, 8.91vs. 9.09 × 10^6 cells/Kg, *P* = .8435 and 325 vs. 324 minutes, *P* = .9380, respectively). Therefore, the effect of diabetes, radiation therapy, and lytic lesions on collection yield and apheresis time were not explored further.

Prolonged Lenalidomide Exposure is Associated With Decreased Pre-Apheresis Counts and Extended Apheresis Requirement

We next examined whether the length of lenalidomide exposure affects factors thought to impact apheresis yield and efficacy. As would be expected, there was no significant correlation between the number of cycles of lenalidomide a patient received and age at first apheresis or bone marrow cellularity at diagnosis (R^2 = 0.02070, *P* = .1666 and R^2 = 0.01563, *P* = .2602, respectively). However, patients who received PInd had significantly lower pre-apheresis platelet counts than patients who received SI (mean 129 vs. 171 k/mcl, *P* = .0103, Figure 1A). Likewise, there was a significant negative correlation between the number of cycles of lenalidomide a patient received and pre-apheresis platelet count (R^2 = 0.05691, *P* = .0206, Figure 1B). A similar pattern was seen in pre-apheresis WBC: patients who received PInd had a lower WBC than patients who received SI (median 6.850 vs. 24.40 k/mcl, *P* = .0063, Figure 1C), and longer lenalidomide induction correlated with reduced WBC (R^2 = 0.05765, *P* = .0212,

Figure 1A Patients who received prolonged induction had reduced pre-apheresis platelet count. Bar graphs represent means with standard error of the mean. 4-6 cycles Lenalidomide Mean (SEM, n): 171 (11.7, 54). >6 cycles Lenalidomide Mean (SEM, n): 129 (9.5, 40). Students t test, 2 sided. * $P < .05$. $P = .0103$.

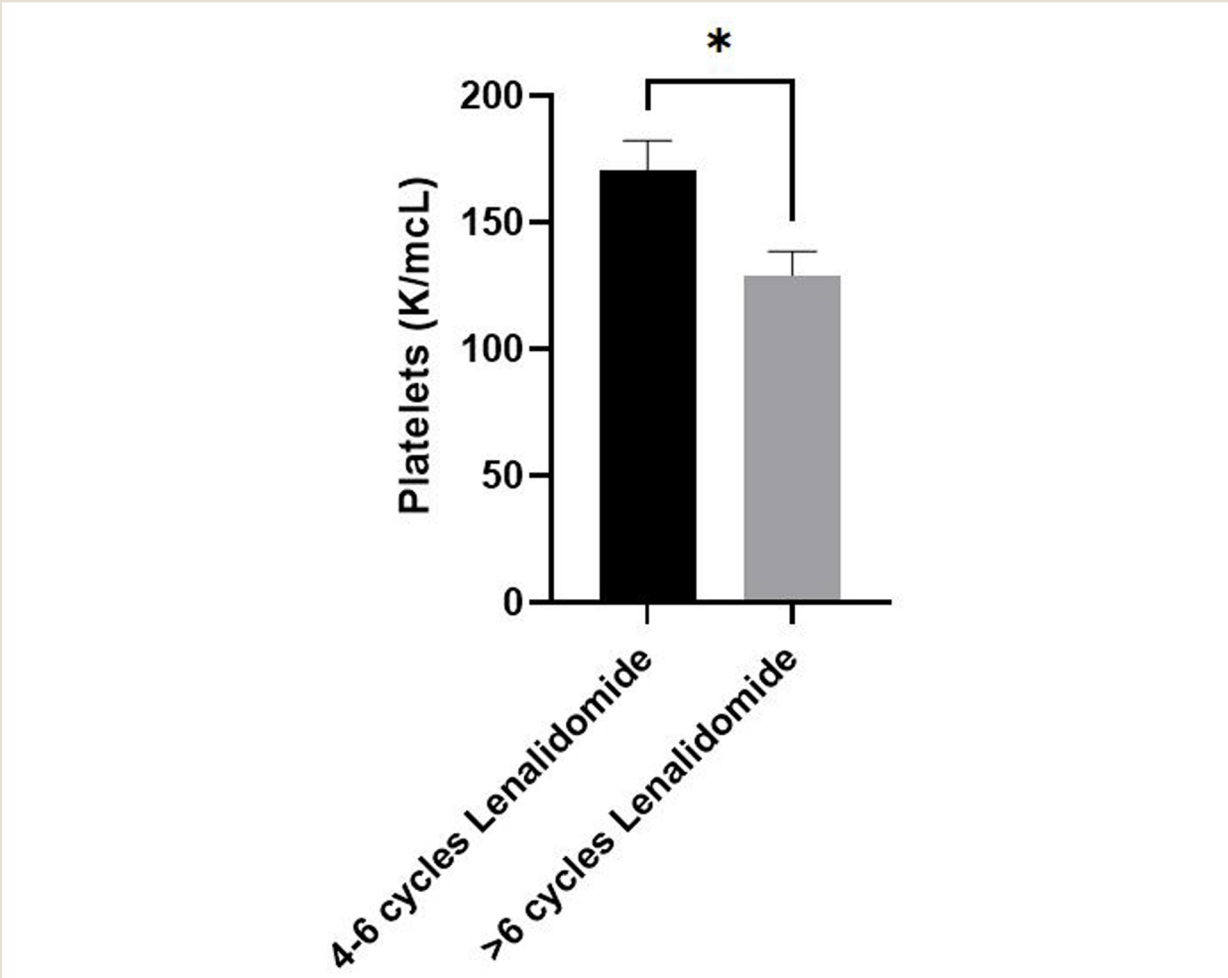


Figure 1D). Intriguingly, there was no correlation between the duration of lenalidomide exposure and the pre-collection peripheral $CD34^+$ cell count ($R^2 = 0.005533$, $P = .4859$), nor was there a significant difference in pre-collection peripheral $CD34^+$ cell counts between SI or PInd cohorts (median 26.90 vs. 28.35, respectively, $P = .9046$). Our results suggest that lenalidomide exposure reduces WBC and platelet count, reflecting evidence of marrow suppression that is still apparent shortly prior to apheresis and after mobilization. However, this effect does not extend to the peripheral $CD34^+$ cell count collected prior to apheresis.

Having established that prolonged lenalidomide exposure is associated with reduced pre-apheresis WBC and platelet count, we investigated whether the duration of lenalidomide exposure is itself associated with collection outcomes. We started with apheresis time. Patients who received PInd were significantly more likely than patients who received SI to require 2 or more days of apheresis (38% vs. 15%; OR 3.45; 95% CI 1.323- 9.471; $P = .0154$), suggesting they required longer to reach the stem cell collection target. Patients who received PInd underwent significantly longer apheresis than patients treated by SI (median 366 vs. 316.5 minutes, $P = .0380$, Figure 2A). There was also a significant positive correlation between the number of cycles of lenalidomide and minutes of apheresis (A_{Min}) ($R^2 = 0.06423$, $P = .0148$, Figure 2B).

Although SI and PInd cohorts were well balanced with respect to the use of cyclophosphamide, plerixafor, or both (Table 1), analysis of whether duration of lenalidomide exposure prolonged apheresis independently of its impact on pre-apheresis counts would likely be complicated by the heterogeneity in mobilization strategies. Instead, we therefore investigated whether duration of lenalidomide exposure was associated with the likelihood of requiring 2 or more days of apheresis while controlling for age, bone marrow cellularity, and pre-apheresis peripheral $CD34^+$ cell count (Table 3). By multivariate logistic regression analysis, only the number of cycles of lenalidomide and the pre-apheresis peripheral CD34+ cell count were independently associated with requiring more than 1 day of apheresis (Table 3). In particular, each additional cycle of lenalido-

Figure 1B Lenalidomide exposure correlates with reduced pre-apheresis platelet count.

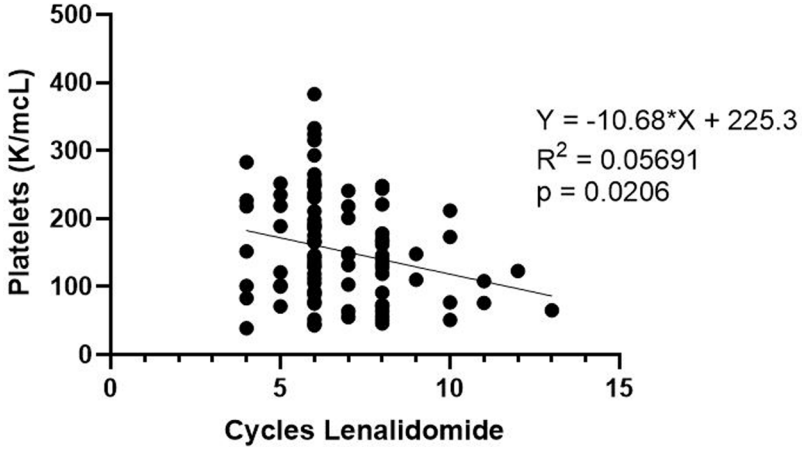


Figure 1C Patients who received prolonged induction had reduced pre-apheresis WBC. Bar graphs represent medians with 95% CI. 4-6 cycles Lenalidomide median (95% CI): 24.40 (8.90-30.00). >6 cycles Lenalidomide median (95% CI): 6.850 (5.20-14.70).Mann-Whitney test, 2 sided. ** $P < .01$. $P = .0063$.

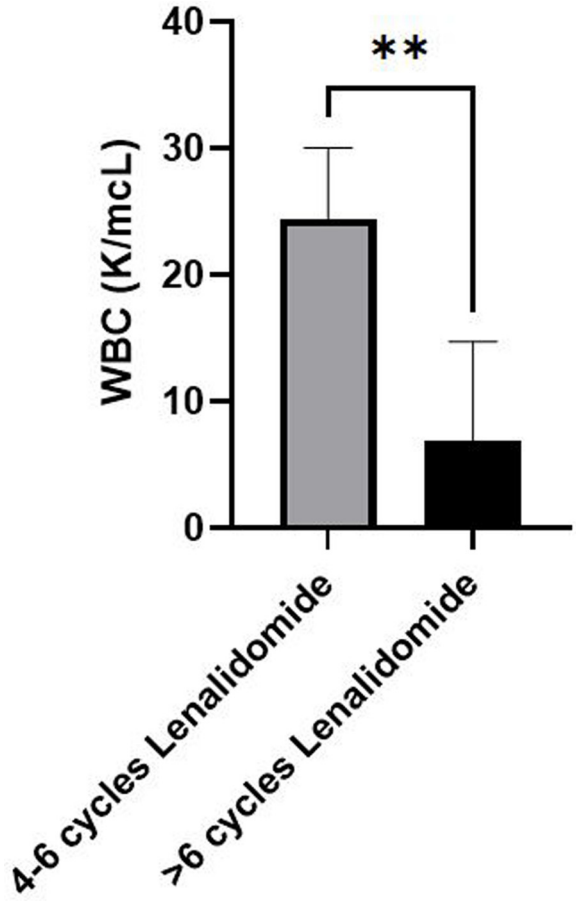


Figure 1D Lenalidomide exposure correlates with reduced pre-apheresis WBC.

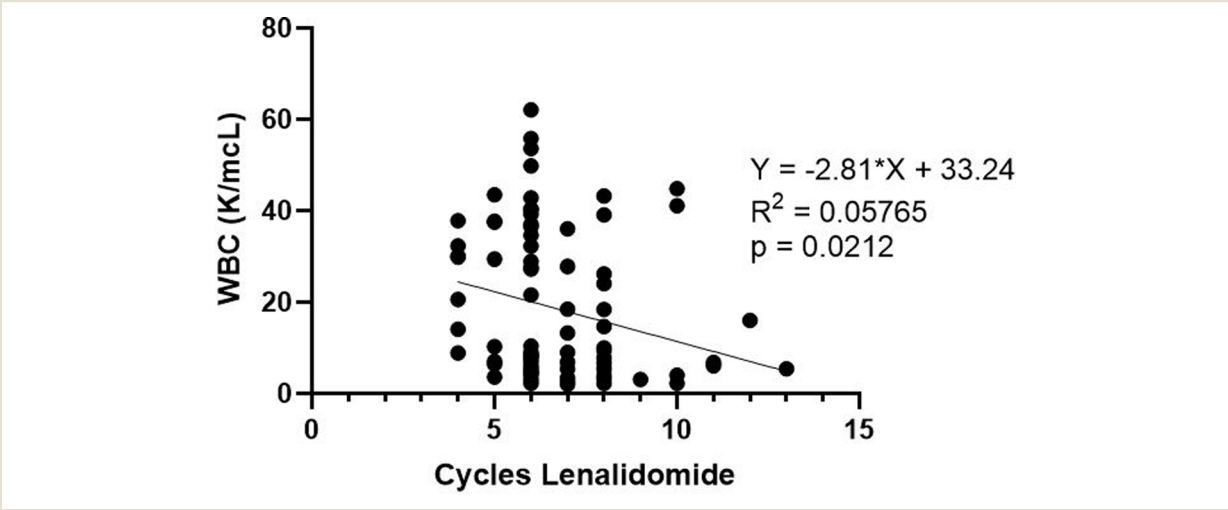


Table 3 Multivariate Logistic Regression for Multiple Days of Apheresis

Multiple Days Of Apheresis Predicted By Cycles Lenalidomide, Age, Bone Marrow Cellularity, And Peripheral CD-34 Probability modeled: "Patient received more than 1 day of apheresis".		
Independent variable	**Odds ratio (95% confidence interval)**	***P* value**
Cycles lenalidomide	1.581 (1.109 to 2.370)	.0157
Age (at apheresis)	0.9778 (0.8957 to 1.067)	.6104
Bone marrow cellularity (at diagnosis)	1.004 (0.9771 to 1.031)	.7826
Peripheral CD34+ Cells (pre-apheresis)	0.9411 (0.8995 to 0.9736)	.0025

mide was associated with increased likelihood of requiring multiple days of apheresis (odds ratio = 1.581, 95% confidence interval 1.109-2.370).

Prolonged Lenalidomide Exposure Does Not Reduce Stem Cell Yield in Patients Mobilized With Cyclophosphamide or Plerixafor

To directly investigate the effect of duration of lenalidomide exposure on $CD34^+$ cell yield, we examined the total $CD34^+$ cells collected (C_T) and the $CD34^+$ cells collected on the first day of apheresis (C_{D1}). There was no significant difference between patients who received SI with 4-6 cycles of lenalidomide or PInd with >6 cycles of lenalidomide in C_{D1} (mean 9.59 vs. 8.29, $P = .1788$, Figure 2C) or C_T (mean 10.46 vs. 9.99, $P = .5513$, Figure 2D). There was also no significant correlation between the number of cycles of lenalidomide and C_T ($R^2 = 0.008344$, $P = .3812$) or C_{D1} ($R^2 = 0.02102$, $P = .1633$). Further, SI and PInd groups did not differ significantly in the frequency of patients collecting $\geq 8 \times 10^6$ $CD34^+$ cells/Kg, sufficient for 2 transplants per our institutional protocol (76% vs. 65%, respectively, $P = .2599$). Due to the heterogeneous mobilization strategies present in our cohorts, we also investigated whether the lack of effect of lenalidomide exposure on stem cell yields persisted when patients were grouped by mobilization strategy. Among those patients who received mobilization with plerixafor and G-CSF (39, 41%), there was still no significant difference between those patients who received SI or PInd with respect to C_T (9.81 vs. 10.08×10^6 cells/Kg, $P = .7897$) or C_{D1} (7.43 vs. 8.63×10^6 cells/Kg, $P = .3291$). Likewise, there was no correlation between the number of cycles of lenalidomide and C_T ($R^2 = 0.01180$, $P = .4255$) or C_{D1} ($R^2 = 0.02874$, $P = .2117$). Among patients that received induction with cyclophosphamide and G-CSF (38, 40%), there was no significant difference between those patients who received SI or PInd with respect to C_T (10.23 vs. 11.05×10^6 cells/Kg, $P = .5249$) or C_{D1} (9.44 vs. 11.00×10^6 cells/Kg, $P = .2687$). Likewise, there was no correlation between the number of cycles of lenalidomide received and C_T ($R^2 = 0.004839$, $P = .6781$) or C_{D1} ($R^2 = 0.01488$, $P = .4656$).

These findings suggest that ultimately, the impact of prolonged lenalidomide exposure on stem cell yield is minimal when mobilization is augmented with cyclophosphamide and/or plerixafor. However, although we did not observe a significant correlation between the duration of lenalidomide treatment and either C_T or C_{D1}, there was a trend toward a negative correlation between C_{D1} and cycles of lenalidomide ($R^2 = 0.02102$, $P = .1633$). We therefore performed multivariate regression to further characterize the relationship between C_{D1} and cycles of lenalidomide.

Figure 2A Patients who received prolonged induction had longer apheresis time. Bar graphs represent medians with 95% CI. 4-6 cycles Lenalidomide median (95% CI): 316.5 (280-329). >6 cycles Lenalidomide median (95% CI): 366 (324-516). Mann-Whitney test, 2 sided. * $P < .05$. $P = .0380$.

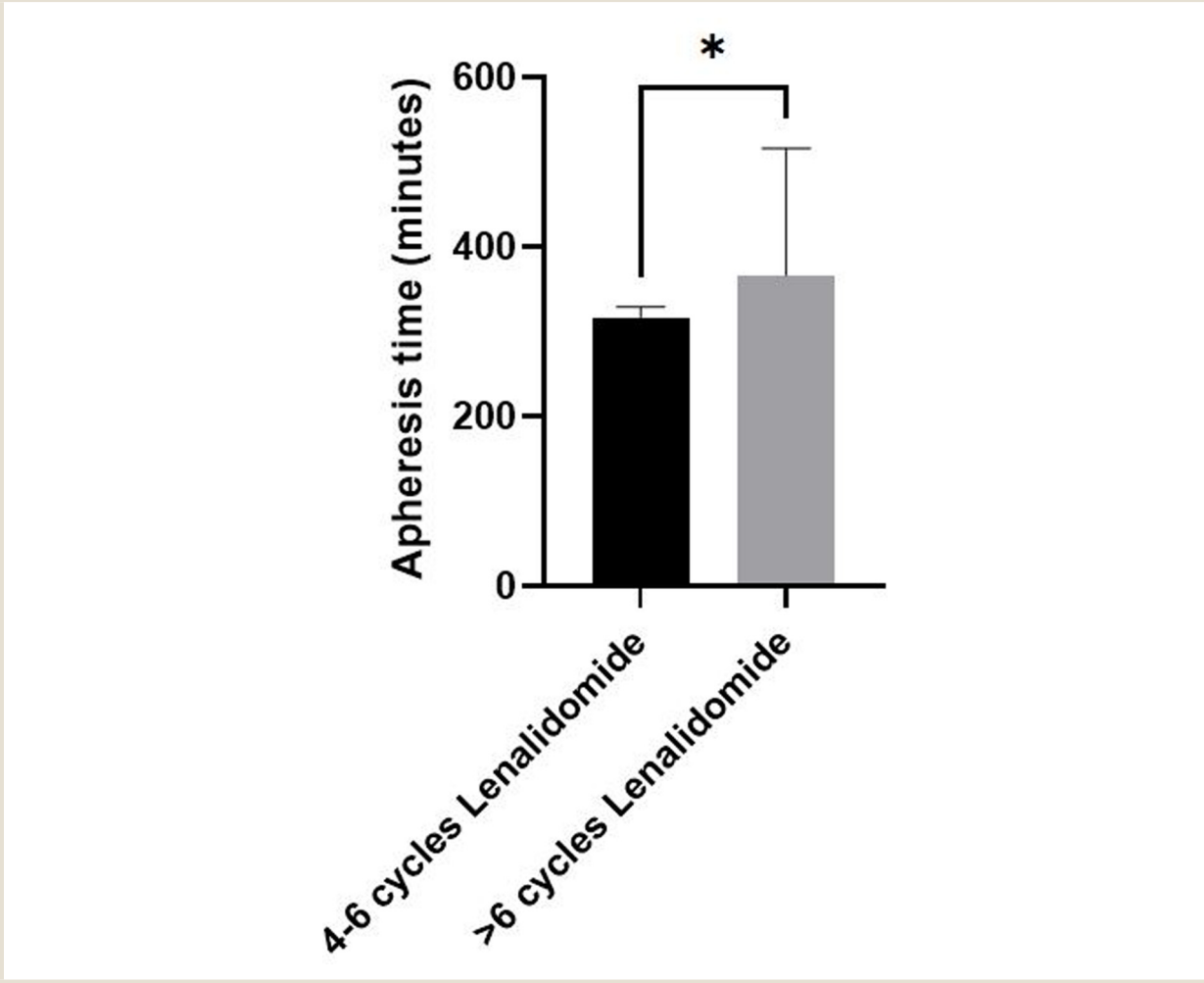


Figure 2B Lenalidomide exposure correlates with apheres time.

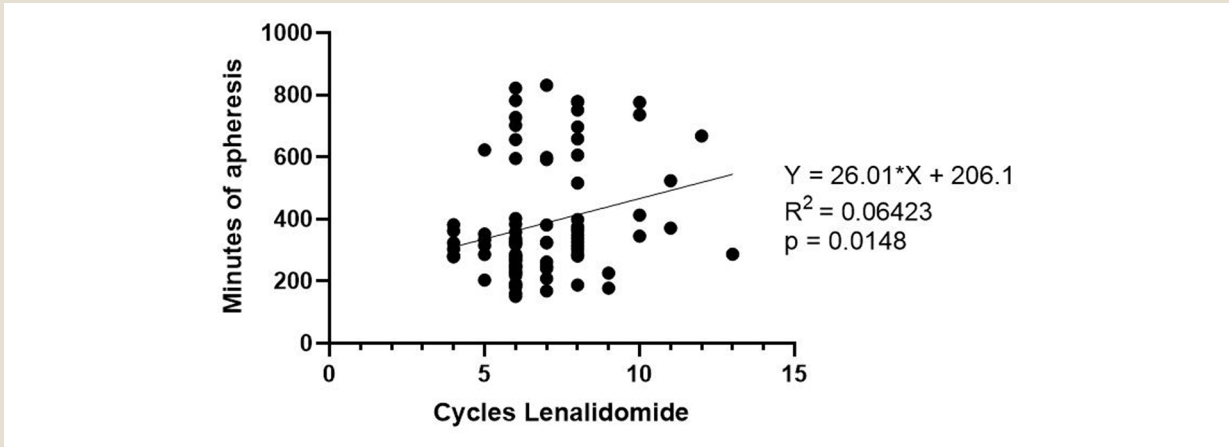
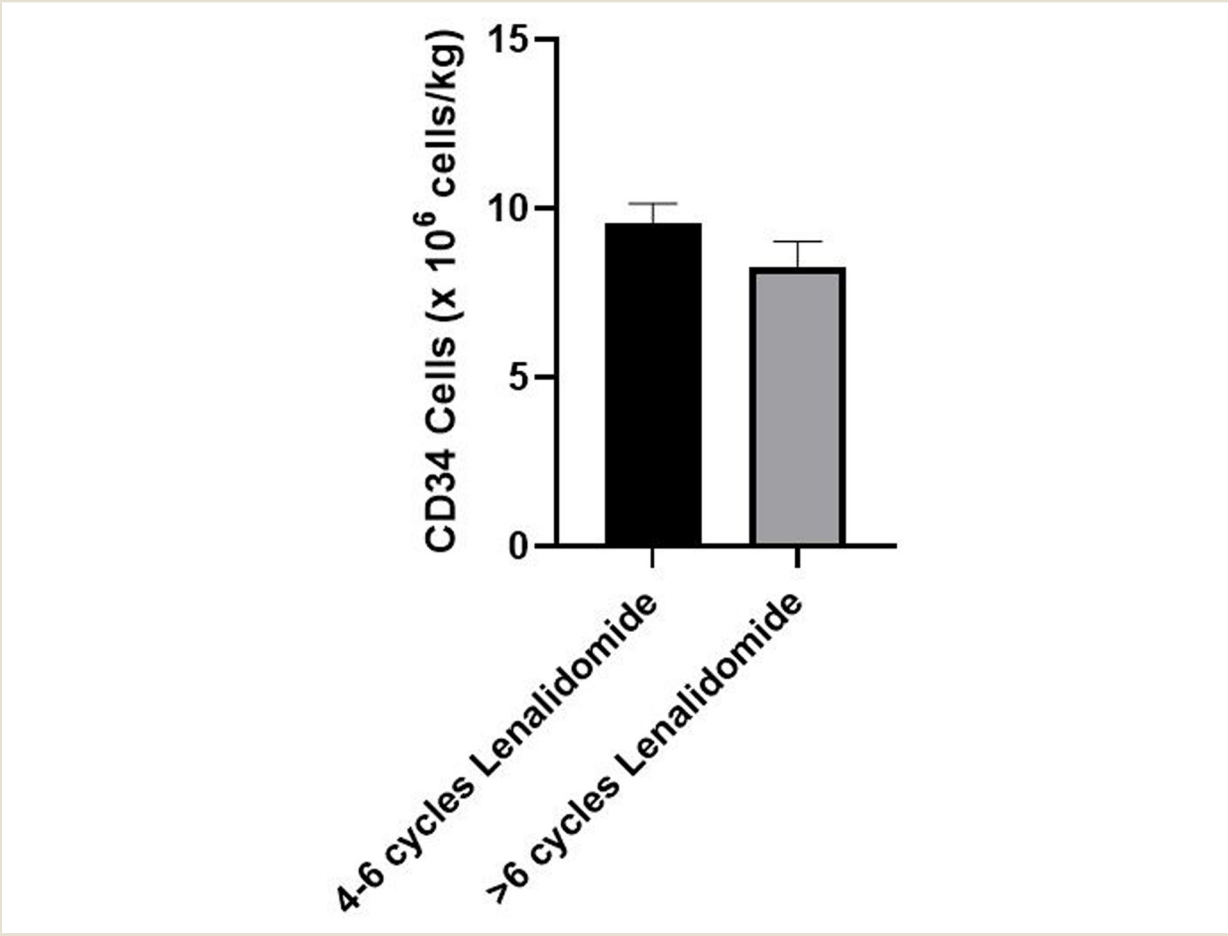


Figure 2C Prolonged induction did not affect first day stem cell yield. Bar graphs represent means with standard error of the mean. 4-6 cycles Lenalidomide Mean (SEM): 9.59 (0.5966). >6 cycles Lenalidomide Mean (SEM): 8.29 (0.7290). Students t test, 2 sided. $P = .1788$.



We selected age at first apheresis, pre-apheresis platelet count, and pre-apheresis peripheral $CD34^+$ cell count as covariates, as each significantly correlated with C_{D1} cell yield in univariate analysis (Table 2).

We could not identify a significant effect of lenalidomide exposure on $C_{D1,}$ neither by the number of lenalidomide cycles ($\beta = -0.2411$, $P = .3004$) nor by PInd with > 6 cycles of lenalidomide ($\beta = -0.6024$, $P = .4655$) (Table 4). Pre-apheresis platelet count and pre-apheresis peripheral CD34 count remained significant predictors of C_{D1} in both models (Table 4). We also performed multivariate linear regression using the same set of predictors with C_T as an outcome variable, although a correlation between C_T and cycles of lenalidomide was not expected based on the results of univariate analysis ($P = .3812$). Neither the number of cycles ($\beta = -0.09715$, $P = .6300$) nor prolonged induction ($\beta = -0.01842$, $P = .9794$) predicted C_T (Table 5). The effect of platelets was no longer significant, though age and pre-apheresis peripheral $CD34^+$ cell count were significant predictors of total $CD34^+$ stem cell yield (Table 5).

Discussion

Early in the COVID-19 pandemic, our center delayed mobilization and transplantation to minimize patient exposure and risk, and recommended continuing induction therapy. As the pandemic stretched on and we found we were able to safely support patients through mobilization and transplantation, our practice shifted back to standard induction. Thus, since the start of the pandemic, we have mobilized many patients after PInd and after SI, providing an opportunity to examine how the duration of lenalidomide induction affects $CD34^+$ cell colletion. Within a patient population mobilized exclusively with the assistance of plerixafor or cyclophosphamide, we found no compelling evidence that the duration of lenalidomide treatment affects $CD34^+$ stem cell yields or that prolonged induction with >6 cycles of lenalidomide precludes successful collection of sufficient mobilized stem cells for transplant. However, we identified an association between longer lenalidomide induction and longer apheresis times, and longer lenalidomide exposure increased the risk of requiring more than one apheresis session.

Figure 2D Prolonged induction did not affect total stem cell yield. Bar graphs represent means with standard error of the mean. 4-6 cycles Lenalidomide Mean (SEM): 10.46 (0.4958). >6 cycles Lenalidomide Mean (SEM): 9.99 (0.6128). Students t test, 2 sided. $P = .5513$.

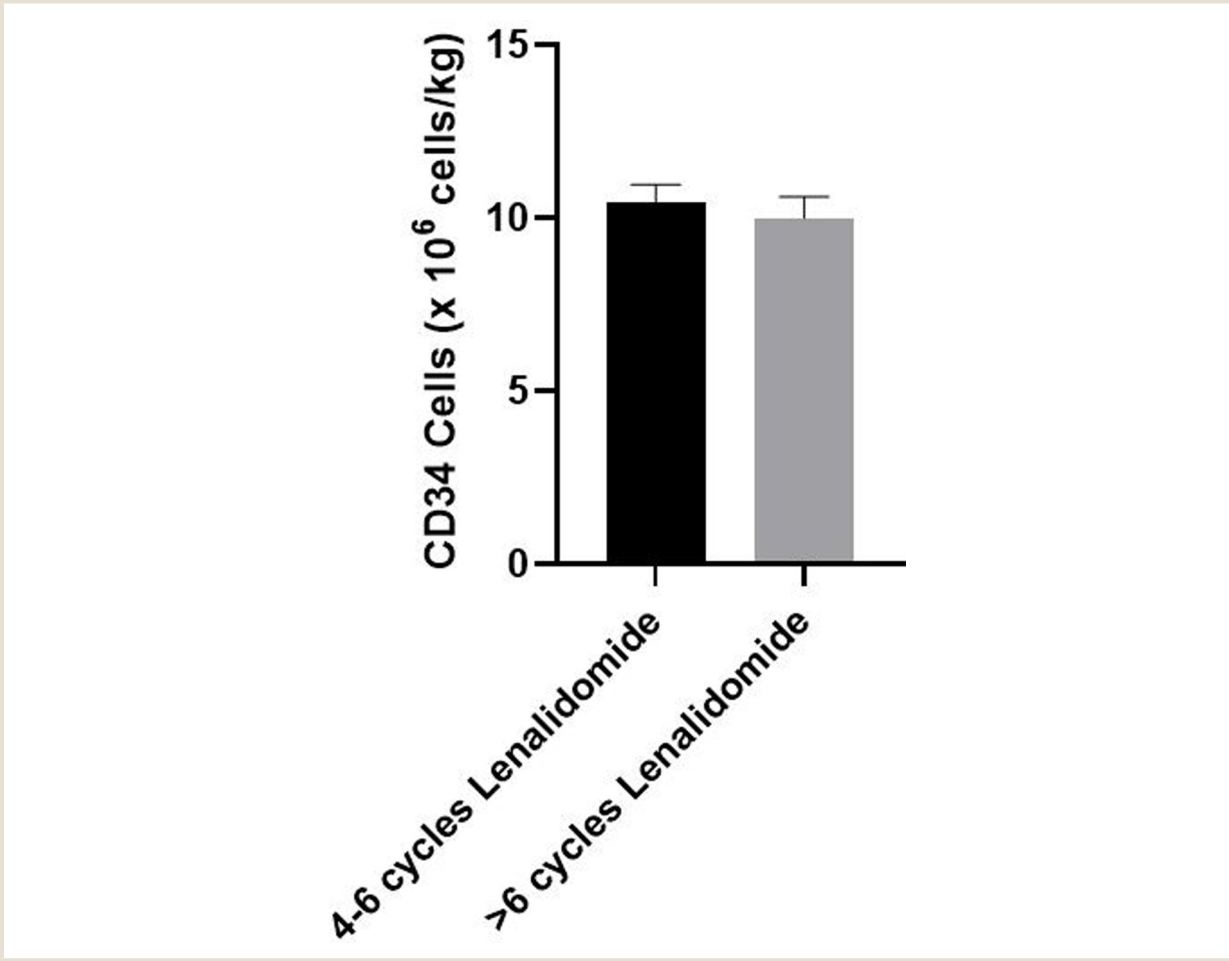


Table 4 Multivariate Linear Regression for Day 1 Apheresis Yield (C_{D1})

Day 1 Apheresis Yield (C_{D1}) Predicted By Cycles of Lenalidomide, Platelets, Age, And Peripheral CD-34		
Independent Variable	**β estimate (Standard Error)**	***P* value**
Cycles lenalidomide	-0.2411 (0.2315)	.3004
Platelets (pre-apheresis)	0.01565 (0.005245)	.0037
Age (at first apheresis)	0.01265 (0.04827)	.7938
Peripheral CD34+ Cells (pre-apheresis)	0.04000 (0.006858)	<.0001
Day 1 apheresis yield (C_{D1}) predicted by Prolonged or Standard induction, platelets, age, and peripheral CD-34		
Independent variable	β estimate (standard error)	*P* value
Standard Induction (4-6 cycles of L)	1 (reference value)	NA
Prolonged Induction (> 6 cycles of L)	-0.6024 (0.8218)	.4655
Platelets (pre-apheresis)	0.01587 (0.005301)	.0036
Age (at first apheresis)	0.01032 (0.04832)	.8313
Peripheral CD34+ Cells (pre-apheresis)	0.03980 (0.006879)	<.0001

Table 5 . Multivariate Linear Regression for Total CD34 Apheresis Yield (C_T)

Total Apheresis Yield (C_T) Predicted By Cycles Of Lenalidomide, Platelets, Age, And Peripheral CD-34		
Independent Variable	**β estimate (Standard Error)**	***P* value**
Cycles lenalidomide	-0.09715 (0.2010)	.6300
Platelets (pre-apheresis)	0.004502 (0.004554)	.3256
Age (at first apheresis)	-0.09602 (0.04190)	.0243
Peripheral CD34+ Cells (pre-apheresis)	0.02606 (0.005954)	<.0001
Total apheresis yield (C_T) predicted by Prolonged or Standard induction, platelets, age, and peripheral CD-34		
Independent variable	β estimate (standard error)	*P* value
Standard Induction (4-6 cycles of L)	1 (reference value)	NA
Prolonged Induction (>6 cycles of L)	-0.01842 (0.7122)	.9794
Platelets (pre-apheresis)	0.004945 (0.004594)	.2847
Age (at first apheresis)	-0.09812 (0.04187)	.0213
Peripheral CD34+ Cells (pre-apheresis)	0.02601 (0.005962)	<.0001

Our findings are consistent with a growing literature that suggests plerixafor and cyclophosphamide mobilize sufficient cells for transplant in the vast majority of patients, including those treated with prolonged lenalidomide induction. The initial studies describing a significant inhibitory effect of lenalidomide on stem cell collection were performed in patients mobilized mostly with G-CSF alone.[7-13] Later studies that included patients who were treated with lenalidomide induction and mobilized with the addition of cyclophosphamide[15-19] or plerixafor[20-23] demonstrated a significant improvement in stem cell yield such that most patients were able to collect sufficient cells for transplant. These studies did not specifically investigate whether prolonged induction with lenalidomide affects stem cell collection, as lenalidomide induction is typically capped at 6 cycles. However, in another retrospective study, Cowan and colleagues recently reported their findings that higher lenalidomide exposure did not significantly reduce stem-cell yield following mobilization, whether with G-CSF alone or combined with chemotherapy or plerixafor.[24] Our findings are consistent with their report. However, our study differed by only including patients mobilized with the addition of cyclophosphamide or plerixafor, and as such our results describe optimal collection yields that can be expected in the setting of prolonged induction. We also identified a relationship between prolonged lenaldiodide exposure and the amount of apheresis time, whether measured in minutes or the number of apheresis sessions required to collect sufficient $CD34^+$cells. Prior studies have differed with respect to whether the duration of lenalidomide correlates with apheresis time,[23,24] and it is possible that institutional specific factors contribute to the discrepancies.

The effect of prolonged lenalidomide treatment on successful stem cell mobilization and harvest for ASCT has significant clinical importance. Response to induction deepens with increasing cycles,[25] which cautions against very short induction regimens. Recently, a large randomized phase III trial demonstrated that treatment with lenalidomide delays progression of intermediate- or high-risk smoldering multiple myeloma.[37] Although patients were advised to collect stem cells for possible ASCT after 4-6 cycles of lenalidomide, the median number of cycles of lenalidomide patients ultimately received was greater than 20.[37] As the results of this paradigm shifting trial are widely adopted, we can expect that more patients may present for stem-cell mobilization with significant lenalidomide exposure. Our findings still support early mobilization and collection of stem cells after 4-6 cycles of lenalidomide, as this will likely permit many to mobilize successfully without chemotherapy or plerixafor. Our findings also suggest that early moblilization will require fewer apheresis procedures. However, clinicians can be reassured by our results that augmented mobilization with chemotherapy and/or plerixafor will likely allow for successful stem-cell harvest even after prolonged lenalidomide exposure. Our report also suggests that moderate extension of induction therapy, in the setting of future pandemics or logistical obstacles, is unlikely to compromise the ability to collect sufficeint stem cells for transplant.

Our work has the inherent limitations of a single-center retrospective analysis. It is possible that our study of 94 patients, including 40 who had prolonged lenalidomide-based induction with more than 6 cycles, was not adequately powered to detect small effect sizes. Only 10 patients received 9 or more cycles, and thus our results may be less applicable to patients who receive highly prolonged treatment with lenalidomide. Of note, there is a case report in which a patient who received 68 cycles of lenalidomide was successfully mobilized with G-CSF and plerixafor,[38] which suggests that even exceptionally prolonged lenalidomide induction does not preclude successful mobilization and harvest. Our study included 5 patients older than 70, and our oldest patient was only 72 at the time of apheresis. ASCT significantly extends survival in patients 74 years of age or older,[39] but since our study included no patients in this age group, our results may not be generalizable to this population. Nonetheless, in our analysis, age at first apheresis was significantly negatively associated with total stem cell yield, suggesting that efforts to optimize mobilization and collection, including mobilization early in the treatment course, employment of augmented mobiliza-

tion strategies, and planning for multiple-day collections, may be necessary to optimize successful harvest in patients with advanced age.

In conclusion, prolonged lenalidomide induction in patients mobilized with cyclophosphamide or plerixafor may increase the apheresis time required to collect sufficient $CD34^+$ cells for ASCT but does not ultimately reduce the total number of stem cells collected. Our work provides re-assurance that clinicians may extend lenalidomide induction, when necessary, without significantly compromising the ability to collect sufficient stem cells for transplant.

Clinical Practice Points

- Induction with lenalidomide impairs stem cell collection in multiple myeloma patients mobilized with G-CSF alone, and therefore lenalidomide induction is traditionally capped at 6 cycles. The addition of cyclophosphamide or plerixafor to mobilization regimens allows the majority of lenalidomide-treated patients to collect sufficient cells for autologous stem cell transplantation (ASCT). Whether prolonged induction with more than 6 cycles of lenalidomide significantly impairs stem cell collection in patients mobilized with cyclophosphamide or plerixafor has been inadequately explored.
- Initially, the COVID-19 pandemic created a need to defer mobilization and transplantation to minimize patient exposure and risk; this resulted in an opportunity to study the impact of prolonged lenalidomide induction on our ability to collect sufficient stem cells to permit ASCT following augmented mobilization with cyclophosphamide or plerixafor.
- Longer induction with lenalidomide was associated with longer apheresis times and a higher likelihood of requiring more than 1 session of apheresis to collect adequate $CD34^+$ cells for ASCT. However, ultimately the $CD34^+$ stem cell yield was not affected by the duration of lenalidomide exposure.
- Patients and clinicians can be re-assured that prolonged induction with lenalidomide is unlikely to compromise the ability to harvest sufficient stem cells for transplant, though longer apheresis time might be anticipated, and patients should receive plerixafor or cyclophosphamide as part of their mobilization regimen.
- Clinicians can expect that the majority of patients who receive prolonged courses of lenalidomide, due to treatment of smoldering myeloma, future pandemics, or patient preference will be able to collect sufficient cells for transplant.

Disclosure

The authors have stated that they have no conflicts of interest.

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