Clinical outcomes of multiple myeloma patients who undergo autologous hematopoietic stem cell transplant with G-CSF or G-CSF and plerixafor mobilized grafts

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Abstract

Impact of Plerixafor (P) mobilized stem cells on immune reconstitution, such as absolute lymphocyte count at day 30 (ALC30), and on long-term outcomes of Multiple Myeloma (MM) patients undergoing autologous stem cell transplant (ASCT) has not been well established. We evaluated total of 469 patients mobilized with G-CSF (G) alone and 141 patients mobilized with G-CSF plus plerixafor (G+ P). Patients only received plerixafor if they had peripheral blood CD34+ve blood count < 20/uL on first planned day of collection. Primary endpoint, ALC30, was 1.3 K/uL (range, 0.1–4.5) and 1.2 K/uL (range, 0.1–5.1) for G and G+P, respectively (p=0. 61). The median PFS was 2.5 years (95% CI, 2.1–3.2) and 2.8 years (95% CI, 2.0–3.3) for G and G + P, respectively (HR: 1.13; 95% CI, 0.84–1.50; p=0. 42). The median OS was 6.1 years (95% CI, 4.6-NR) for G group compared to 3.7 years (95% CI, 3.2-NR) for the G+P group (HR: 1.64; 95% CI, 1.12–2.40; p=0. 01). The median follow-up time for OS was 2.53 years (95% CI, 2.13–2.99) and 1.59 years (95% CI, 1.17–2.02) for G and G+ P group, respectively. In this large retrospective analysis of MM patients mobilized with G-CSF vs G-CSF + P, there was no significant difference in lymphocyte recovery or PFS. There was an overall survival difference in patients who were poor mobilizers and could not be mobilized with G-CSF alone.

Keywords

G-CSF; Plerixafor; Multiple Myeloma; Autologous stem cell transplant

Introduction

High-dose therapy followed by autologous stem cell transplantation (ASCT) remains a standard of care in eligible patients undergoing treatment for multiple myeloma (MM). Approximately 20% of the MM patients undergoing mobilization of peripheral blood stem cells (PBSC) with granulocyte colony stimulating factor (G-CSF) alone or G-CSF plus

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chemotherapy are not able to mobilize the minimum number of CD-34+ stem cells (2 X 10^6 CD34 cells/kg) recommended for transplant [1, 2]. Plerixafor (P) is a reversible direct antagonist of CXCR4/SDF-1, which prevents binding of its ligand CXCL12 and induces mobilization of cells expressing this receptor, including hematopoietic stem and progenitor cells (HSPCs) [3]. Based on a pivotal randomized phase-3 study comparing G-CSF vs G-CSF plus plerixafor, plerixafor has been approved for mobilization of PBSCs in MM by the Food and Drug Administration [4]. However, because the true benefit of plerixafor use is mainly seen in patients who are poor mobilizers and increased cost associated with its use, a risk-adapted approach for plerixafor use (using plerixafor in only poor mobilizers such as patients who after 5 days of G-CSF have a peripheral CD34+ve cells count of < 20 cells/μL) is in practice at many centers, including ours [5, 6].

Peripheral blood stem cell grafts collected with plerixafor contain more natural killer (NK) cells, T cells (CD3, CD4), primitive CD-34 cells, mature lymphocytes, dendritic cells and repopulating cells compared to grafts collected with G-CSF alone [7, 8]. Higher amounts of CD-34+ cells infused at transplant have been associated with improved survival in multiple studies [9, 10]. It is also hypothesized that the use of plerixafor can improve lymphocyte recovery post-transplant through mobilization of more mature lymphocytes [11, 12]. Early lymphocyte recovery (absolute lymphocyte count, ALC-30, of > 1,000/μL at day 30 after transplant) has been shown to predict improved PFS in MM patients [12–14]. No major difference has been observed in terms of engraftment of neutrophils and platelets in MM patients undergoing mobilization with G-CSF plus plerixafor compared to G-CSF alone in randomized studies [4, 15, 16]; however, ALC-30 has not been well studied in the context of plerixafor use for MM.

Long term follow-up of the patients from the pivotal phase-3 trial comparing the G and G+P groups showed similar 5-year OS and PFS in MM [17]. However, it is unclear if the long-term outcomes (PFS and OS) would be different if the mobilization agent is determined based on a risk-adapted approach. With this study, we retrospectively evaluated the short-term outcomes such as engraftment including lymphocyte recovery (ALC-30) and long-term outcomes of PFS and OS in a large group of MM patients undergoing ASCT with PBSCs mobilized with G-CSF (G) and G-CSF plus Plerixafor (G+P) where plerixafor was administered when the peripheral CD-34+ cell-count was < 20/uL on day 5 of G-CSF use.

Methods

Patients

We conducted a retrospective study of patients who underwent their first ASCT for diagnosis of MM with either G-CSF or G-CSF plus plerixafor mobilized stem cells at Karmanos Cancer Institute. Patients in whom GM-CSF was used for mobilization were excluded from this study. This study was approved by Wayne State University Intuitional Review Board.

Karmanos Cancer Center Blood and Marrow Stem Cell Transplant Program prospectively collected relevant data in all patients who received stem cell transplantation for reporting to the Center for International Blood and Marrow Transplant Research (CIBMTR). This study

was the outcome analysis of retrospective retrieval of collected details regarding patient demographics, disease status and transplant outcomes. International Staging System (ISS) was used for initial staging and International Myeloma Working Group (IMWG) Uniform Response criteria was used to group patients in CR, VGPR, PR, SD or PD at the time of transplant [18]. Patients who had CR, VGPR or PR were considered to have "response" and patients with SD and PD were considered to have "no response". Information regarding significant co-existing disease (defined as more than one or multiple chronic or long-term diseases/conditions), total lines of treatment before transplant (one or more), utilization of a doublet vs triplet therapy approach and post-transplant maintenance was also collected. No patients in this study received a tandem transplant.

Mobilization and Preparative Regimen

Per institutional guidelines, the goal for mobilization was to collect PBSCs for two autologous transplants with the minimum collection of 4 X 10^6 CD34 cells/kg. All patients received G-CSF 10mcg/kg/day for five days subcutaneously until the first planned day of apheresis. Plerixafor 240 mcg/kg was administered when the peripheral CD-34+ cell-count was < 20/ uL on day 5 of G-CSF use. All patients received Melphalan conditioning either at 140 or 200 mg/m^2 at treating physician's discretion based on co-morbidities and functional status. Per institutional policy, Melphalan140 mg/m^2 was used for pts > 65 years, those with significant comorbidities and imapired renal function.

Engraftment

Neutrophil engraftment was defined as the first of the 3 consecutive days with absolute neutrophil count greater than 0.5 X10^9/L (ANC500) without growth factor support and platelet engraftment was defined as platelet value of greater than 20 X 10^9/L (PLT20) without transfusion support for 7 consecutive days per Center for International Blood and Marrow transplant Research (CIBMTR) definitions. ALC-30 was defined as absolute lymphocyte count at day 30 (+/−7days).

Outcome Measures

The primary end point was to compare the absolute lymphocyte count at day 30 post-transplant (ALC-30) between the G and G+P groups. Secondary end points were to compare the PFS and OS between the two groups and to evaluate the associations between predefined factors (age, race, stage at diagnosis, melphalan dose, disease status at transplant, ALC30, post-transplant maintenance, pre-transplant induction with doublet or triplet therapy, lines of treatment prior to transplant) and outcomes (PFS and OS). The distribution for the cause of death was compared between the two groups.

Statistical Analysis

Baseline patient characteristics were summarized using count and percentage for categorical variables and median and range for continuous variables. Patient baseline characteristics were further compared between two groups of patients with G and G+P. Kruskal-Wallis tests were used to compare two groups for continuous variables and Chi-squared or Fisher's exact tests for categorical variables. OS was calculated as the time from the date of transplantation

to death from any cause. Patients who were alive were considered censored at the date of last observation. PFS was calculated as the time from the date of transplantation to the date of progression or death from any cause. Patients who were alive without progression were considered censored at the date of last observation. Univariable and multivariable Cox proportional hazards regression models were fit to assess associations between nine pre-defined predictors (age, race, stage at diagnosis, melphalan dose, disease status at transplant, ALC30, post-transplant maintenance, doublet/triplet therapy, lines of treatment, G vs G+P group) and outcomes (PFS and OS). The proportional hazards assumption was assessed, and no violation was found.

Results

Baseline Characteristics

Six-hundred and ten patients underwent ASCT between January 2008 and December 2016. Mobilization agents used were G-CSF alone (n= 469) or G-CSF plus plerixafor (n= 141) (Table 1). Median age of patients who were mobilized with G+P was older than those who were mobilized with G only (62 vs. 60 years, p = 0.006). Distribution of patients with respect to sex, race (Caucasian vs non-Caucasians), co-morbidities, ISS Staging (I, II, III) and response to induction therapy before transplant was similar between the two groups (Table 1). Triplet induction therapy (82 vs. 72%, p = 0.015) and more lines of treatment (33 vs. 20%, p = 0.003) were more common in the G+P group (Table 1). Use of 200mg/ m^2 dose of Melphalan (69 vs. 58%, p = 0.020) and a higher dose of CD-34 cells infused (3.19 X 10^6 cells/kg vs. 2.88 X 10^6 cells/kg, p = 0.001) were more common in the G group (Table 1). Post-transplant maintenance treatment use was similar between the two groups. However, use of post-transplant lenalidomide use was less (46 vs 57%, p = 0.034) in the G+P group.

Engraftment Outcomes

The median ALC30 was 1.3 K/uL (range, 0.1–4.5) and 1.2 K/uL(range, 0.1–5.1) for G and G+P groups, respectively (p = 0.608) (Table 1). In addition, absolute monocyte count was similar between the two groups with AMC30 of 0.7 K/uL in both group (p = 0.237). Median day to neutrophil recovery was similar in both groups (ANC 500 at Day 12, p = 0.810) (Table 1). Median day to platelet recovery (PLT20) was 21 days for the G group and 20 days for G+P group (p=.238).

Survival Outcomes

The median PFS was 2.46 years (95% CI, 2.14– 3.15) and 2.77 years (95% CI, 1.99–3.27) for G and G +P, respectively (HR: 1.13; 95% CI, 0.84–1.50; p=0. 417) (Figure 1a). The median follow-up time for PFS was 2.99 years (95% CI, 2.48–3.13) in the G and 1.92 years (95% CI, 1.20–2.53) in the G + P group, respectively. The median OS was 6.09 years (95% CI, 4.55-NR) for G group compared to 3.73 years (95% CI, 3.20-NR) for the G+P group (HR: 1.64; 95% CI, 1.12–2.40; p=0. 011) (Figure 1b). The median follow-up time for OS was 2.53 years (95% CI, 2.13–2.99) and 1.59 years (95% CI, 1.17–2.02) for G and G+ P group, respectively. 115 of 469 patients (25%) in the G group and 35 of 141 patients (25%) in the G+P group had died at the time of the data analysis and the causes of death were similar between the two groups, with disease-related cause being the most common (77% vs

66%), followed by infections (5% vs 1%) and secondary malignancies (4% vs 0%) (Table 2) with a p value of 0.116.

Multivariable Analysis

In multivariable analysis (MVA) with predermined variables as defined in the statistics section, higher stage at diagnosis, less than PR (SD or PD) before ASCT, and no post-transplant maintenance therapy were associated with worse PFS and OS (Table 3). In addition, more than one line of treatment prior to transplant was associated with worse PFS. Use of G+P for mobilization and Melphalan dose of 140 mg/ m^2 were associated with worse OS. ALC-30 >1,000/μL was not associated with difference in PFS or OS in our analysis (Table 3).

Discussion

This study represents a large retrospective study looking at engraftment and survival differences between patients undergoing ASCT for MM with stem cell grafts mobilized with G-CSF vs Poor mobilizers who required use of plerixafor in addition to G-CSF. ALC30, the primary end point of this study, was similar between the two groups. We conclude that the use of plerixafor for augmentation of stem cell mobilization did not alter the ALC30, contrary to the hypothesis that plerixafor can mobilize more lymphocytes [11, 12]. The patient population that received plerixafor in our study was composed of poor mobilizers which could have negated the effect of plerixafor on the mobilization of the lymphocytes as observed in a previous study [19]. An alternative explanation could be that the kinetics of lymphocyte mobilization may be altered due to the use of G-CSF in the previous days. It would be interesting to further analyze the subset of lymphocytes such as natural killer (NK) cells to see whether the combination of G+P can mobilize more NK cells than G alone, as more NK cells have been associated with better survival after transplant [19, 20].

Overall, 141 of 610 (23%) patients in this study were poor mobilizers who required plerixafor as a secondary mobilization agent. This rate of failure of mobilization with G-CSF is similar to previous studies [1, 2]. The extent of prior chemotherapy (time of exposure and lines of treatment) and radiation have been associated with poor stem cell mobilization [21]. In our study, patients who received plerixafor were more likely to have received more than one line of treatment as well as triplet therapy compared to those who received G alone. In addition the median time from diagnosis to transplant was longer in the group that required use of plerixafor by 44 days (274 days vs. 230 days). Older age is a well-recognized risk factor known to cause low yield of PBSCs [22]. Patients who were in G+P group were on average two years older (62 vs 60); however, the difference of 2 years might not be clinically significant.

PFS was similar between the G and G+P groups (30 vs 33.6 months) in this study, despite the fact that patients who required plerixafor had a lower median dose of Melphalan and more previous chemotherapy. Compared to previous small retrospective studies that looked at use of plerixafor in poor-mobilizers (PFS of 22, 21, and 19 months in other studies), the PFS of 33.6 months in our patients who used G+P is superior [8, 23, 24] (Table 4). This

observation could be related to rigorous use of maintenance therapy in our study (at least 67% of the patients).

Infused-CD34 cells were lower by only 0.3 X 10^6 (3.19 X 10^6 vs 2.88 X 10^6) cells/kg after the use of plerixafor in the G+P group which is not be clinically meaningful. Our data supports the use of plerixafor for augmentation in poor-mobilizers, allowing for sufficient CD-34 cells to be collected for the transplant, and these patients can expect similar PFS.

Overall survival of 44 months in this study in the G+P group is comparable to 40 and 53 months seen in previous small studies [23, 24](Table 4). However, OS in our study was worse for group of patients who were poor mobilizers compared to G group (44 months vs 73 months). Melphalan dosing correlated with OS in our multivariable analysis, with improved OS seen in patients receiving 200 mg/ m^2 rather than 140 mg/ m^2 of melphalan. Although use of plerixafor was associated with worse OS in our patient population; this has not been observed in previous studies and could be related to risk-based selection of poor mobilizers for the plerixafor group [8, 23, 24]. Cause of death did not differ between those receiving plerixafor and those who did not. The number of patients in the G+P group who received melphalan does of 200 mg/m^2 and lenalidomide maintenance were lower which have been associated with worse OS. In addition, information regarding treatment at the time of post-transplant progression, which could influence OS, was not available. No patient in the G+P group received a second transplant while 11 patients in the G group received a second transplant

Limitations of this study include its retrospective nature and variation in baseline characteristics of the two groups of patients. Also lack of data on post-transplant progression treatment should be noted, and the association of plerixafor use with OS should be interpreted with caution. Follow-up periods were different for the two groups due to study's retrospective nature and patients could have been exposed to different post-transplant treatments based on drug approvals and practice.

In conclusion, our experience highlights the feasibility of using the day 5 peripheral blood CD-34 count to determine the need for plerixafor in a risk adapted strategy. This strategy is cost effective and provides acceptable PFS in patient who otherwise may not have been able to undergo ASCT due to poor mobilization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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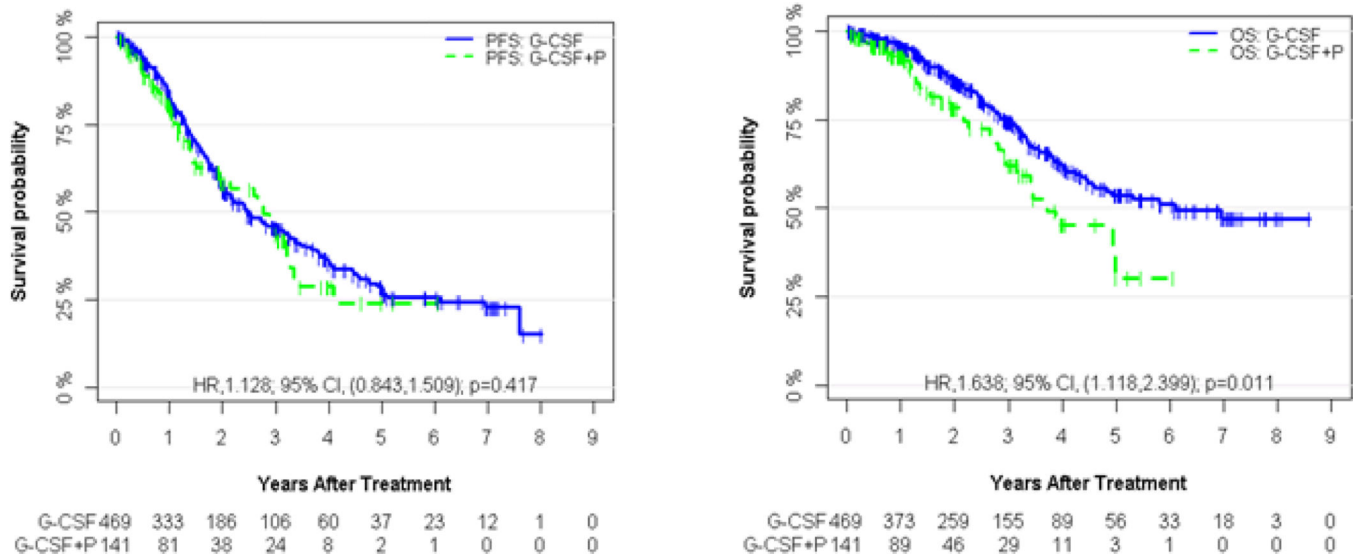
Figure 1.
PFS and OS of G-CSF vs G-CSF + Plerixafor groups. a) Kaplan-Meier curves of progression-free survival (PFS) according to G-CSF and GCSF + Plerixafor (G-CSF+P). The median PFS is 2.46 years (95% CI, 2.14 to 3.15) and 2.77 years (95% CI, 1.99 to3.27) for G-CSF and G-CSF+P, respectively. b) Kaplan-Meier curves of overall survival (OS) according to G-CSF and G-CSF + Plerixafor (G-CSF+P). The median OS is 6.09 years (95% CI, 4.55 to NR) and 3.73 years (95% CI, 3.20 to NR)for G-CSF and G-CSF+P, respectively.

Table 1.

Baseline characteristics of G-CSF vs G-CSF + Plerixafor patients

	G-CSF (N = 469)	G-CSF + Plerixafor (N = 141)	All (N = 610)	Signif.
Age at transplant, year - median (range)	60 (30–76)	62 (41–76)	61 (30–76)	*0.006*
Sex – no. (%)				0.770
Male	274 (58)	85 (60)	359 (59)	
Female	195 (42)	56 (40)	251 (41)	
Race - no. (%)				0.445
Caucasian	330 (70)	107 (76)	437 (72)	
African-American	129 (28)	32 (23)	161 (26)	
Others	10 (2)	2 (1)	12 (2)	
Stage at Diagnosis – no. (%)				>0.99
1	70 (15)	20 (14)	90 (15)	
2	110 (23)	32 (23)	142 (23)	
3	269 (57)	77 (55)	346 (57)	
Unknown	20 (4)	12 (9)	32 (5)	
Disease status at transplant – no. (%)				0.575
CR	77 (16)	21 (15)	98 (16)	
VGPR	153 (33)	47 (33)	200 (33)	
PR	163 (35)	44 (31)	207 (34)	
SD	47 (10)	21 (15)	68 (11)	
PD	28 (6)	8 (6)	36 (6)	
Sig CoExist Disease - no. (%)				0.147
Yes	413 (88)	117 (83)	530 (87)	
No	54 (12)	23 (16)	77 (13)	
Doublet vs Triplet Therapy – no. (%)				*0.015*
Doublet	132 (28)	25 (18)	157 (26)	
Triplet	337 (72)	116 (82)	453 (74)	
Lines of Tx - median (range)	1 (1–6)	1 (1–5)	1 (1–6)	*0.002*
Lines of Tx - no. (%)				*0.003*
1	374 (80)	95 (67)	469 (77)	
>1	95 (20)	46 (33)	141 (23)	
Melphalan (mg/ m^2) - median (range)				*0.020*
140	146 (31)	59 (42)	205 (34)	
200	323 (69)	82 (58)	405 (66)	
Infused CD34 - median X 106(range)	3.19 (1.77–16.9)	2.88 (1.71–7.2)	3.125 (1.71–16.9)	*0.001*
ANC500 (day) - median (range)	12 (10–27)	12 (11–18)	12 (10–27)	0.810
ALC30 (K/uL) - median (range)	1.3 (0.1–4.5)	1.2 (0.1–5.1)	1.3 (0.1–5.1)	0.608
ALC30 (K/uL) - no. (%)				0.369
1	173 (37)	46 (33)	219 (36)	
>1	296 (63)	95 (67)	391 (64)	

	G-CSF (N = 469)	G-CSF + Plerixafor (N = 141)	All (N = 610)	Signif.
Post-transplant maintenance - no. (%)				0.892
Yes	323 (69)	83 (59)	406 (67)	
No	81 (17)	22 (16)	103 (17)	
Unknown	65 (14)	36 (26)	101 (17)	
Post-transplant Lenalidomide - no. (%)				*0.034*
Yes	265 (57)	65 (46)	330 (54)	
No	204 (43)	76 (54)	280 (46)	

Table 2.

Univariable and multivariable Cox regression analyses of factors associated with PFS and OS

		PFS				OS			
		Unadjusted[*]		Adjusted[$]		Unadjusted[*]		Adjusted[$]	
		HR (95% CI)	Signif.	HR (95% CI)	Signif.	HR (95% CI)	Signif.	HR (95% CI)	Signif.
Age									
	<=60	Reference	0.919	Reference	0.416	Reference	*0.012*	Reference	0.176
	>60	0.988 (0.785,1.244)		0.897 (0.691,1.165)		1.519 (1.095,2.107)		1.293 (0.891,1.877)	
Race									
	Caucasian	Reference	0.080	Reference	0.410	Reference	0.681	Reference	0.939
	Others	1.251 (0.974,1.608)		1.125 (0.851,1.487)		1.077 (0.757,1.53)		1.016 (0.684,1.508)	
Stage at diagnosis									
	1	Reference		Reference		Reference		Reference	
	2	1.209 (0.781,1.87)	0.394	1.435 (0.903,2.28)	0.126	2.1 (1.02,4.326)	*0.044*	2.475 (1.153,5.314)	*0.020*
	3	1.826 (1.256,2.655)	*0.002*	1.896 (1.27,2.83)	*0.002*	3.25 (1.701,6.209)	*<0.001*	3.355 (1.679,6.704)	*0.001*
Melphalan dose									
	200	Reference	*0.010*	Reference	0.130	Reference	*<0.001*	Reference	*0.027*
	<200	1.370 (1.077,1.743)		1.238 (0.939,1.631)		2.025 (1.465,2.798)		1.527 (1.049,2.223)	
Disease status at transplant									
	Response	Reference	*0.012*	Reference	*0.014*	Reference	*0.049*	Reference	*0.046*
	Non-Response	1.346 (1.067,1.699)		1.387 (1.07,1.799)		1.39 (1.002,1.93)		1.454 (1.006,2.099)	
ALC30									
	>1	Reference	0.854	Reference	0.896	Reference	0.523	Reference	0.959
	1	1.023 (0.806,1.298)		0.983 (0.759,1.273)		1.114 (0.8,1.549)		0.991 (0.694,1.414)	
Post-transplant Maintenance									
	Yes	Reference	*0.046*	Reference	*0.024*	Reference	*0.009*	Reference	*0.002*
	No	1.378 (1.005,1.888)		1.467 (1.051,2.049)		1.775 (1.151,2.737)		2.075 (1.303,3.304)	
Doublet vs Triplet Therapy									
	Triplet	Reference	0.385	Reference	0.380	Reference	0.385	Reference	0.273
	Doublet	1.115 (0.872,1.427)		1.126 (0.864,1.469)		1.159 (0.831,1.617)		1.224 (0.853,1.755)	
Lines of treatment									
	1	Reference	*<0.001*	Reference	*0.017*	Reference	*0.002*	Reference	0.186
	>1	1.659 (1.288,2.137)		1.413 (1.065,1.874)		1.695 (1.204,2.386)		1.292 (0.884,1.888)	
Group									

	PFS				OS			
	Unadjusted[*]		Adjusted[$]		Unadjusted[*]		Adjusted[$]	
	HR (95% CI)	Signif.	HR (95% CI)	Signif.	HR (95% CI)	Signif.	HR (95% CI)	Signif.
G-CSF G-CSF+P	Reference 1.128 (0.843,1.509)	0.417	Reference 1.084 (0.785,1.498)	0.623	Reference 1.638 (1.118,2.399)	*0.011*	Reference 1.651 (1.089,2.503)	*0.018*

Abbreviations: PFS, progression-free survival; OS, overall survival; HR, Hazard ratio; CI, Confidence interval.

[*], Univariable Cox regression analysis;

[$], Multivariable Cox regression.

Table 3.

PFS and OS in G-CSF vs G-CSF + P groups in other studies

Study	(G-CSF) PFS	(G-CSF) OS	(G-CSF + P) PFS	(G-CSF + P) OS
Moreb et al Ref [23]	-	-	22 months (n=8)	40 months (n=8)
Moreb et al Ref [24]	44 months (n=232)	93 months (n=232)	21 months (n=7)	53 months (n=7)
Valtola et al Ref [8]	13 months (n=20)	-	19 months (n=7)	-
Our Study	30 months (n=469)	73 months (n=469)	33.6 months (n=161)	44 months (n=161)

Table 4.

PFS and OS in G-CSF vs G-CSF + P groups in other studies

Study	(G-CSF) PFS	(G-CSF) OS	(G-CSF + P) PFS	(G-CSF + P) OS
Moreb et al Ref [23]	-	-	22 months (n=8)	40 months (n=8)
Moreb et al Ref [24]	44 months (n=232)	93 months (n=232)	21 months (n=7)	53 months (n=7)
Valtola et al Ref [8]	13 months (n=20)	-	19 months (n=7)	-
Our Study	30 months (n=469)	73 months (n=469)	33.6 months (n=161)	44 months (n=161)